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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶:
C12N 15/12, C07K 14/705, 16/28, C12N 5/10, G01N 33/68

(11) International Publication Number:

WO 99/29847

(43) International Publication Date:

17 June 1999 (17.06.99)

(21) International Application Number:

PCT/US98/23161

A1

(22) International Filing Date:

30 October 1998 (30.10.98)

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

(30) Priority Data:

08/985,809

5 December 1997 (05.12.97)

US Published W

With international search report.

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(54) Title: T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF USING SAME

(57) Abstract

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel and cells and cell lines expressing such nucleic acids. The present invention also provides an isolated or substantially purified T-type calcium channel and an isolated or substantially purified antibody molecule recognizing an epitope on a T-type calcium channel protein.

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T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF USING SAME

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TECHNICAL FIELD OF THE INVENTION

The present invention relates to cloned T-type calcium channels.

BACKGROUND OF THE INVENTION

Biological membranes are themselves generally impermeable to ionic species. Thus, ions enter cells through regulated pores formed from membrane-associated proteins. Most of these regulated pores are voltage-dependent and are thus able to transduce changes in the transmembrane potential into ion flux. Voltage-gated ion channels form a "superfamily" of related proteins (cf. Jan et al., *Nature*, 345, 672 (1990)). Peculiar to this genus is a high degree of conservation in molecular structure. Generally, voltage-gated channels are membrane bound glycolsylated proteins formed of many subunits. Large α subunits form a pore in the membrane that is selective for a given ionic species. Each α subunit contains four domains (I, II, III, and IV). Each channel domain has six putative transmembrane helical segments (S₁-S₆). In general, the segments within each domain are similar but not identical. Aside from overall structural conservation, certain charged residues within the domains are highly conserved among voltage-gated ion channels (Jan et al., *supra*; Stühmer et al., *Nature*, 339, 597-603 (1989)).

Differences in charged residues between groups of voltage-gated ion channels confer properties unique to each subgroup, such as ion selectivity. For example, most voltage gated ion channels are selective for either sodium, potassium or calcium. Known calcium channels require a ring of negative charge provided by glutamate residues found at similar locations in each of the domains (Yang et al., *Nature*, 366, 158-61 (1993)).

Voltage-gated channels are often classified on the basis of their electrophysiology. The resting membrane potential of most animal cells is between about -70 mV and -80 mV. When the membrane becomes depolarized (moved towards 0 mV), various membrane channels become activated (they are said to

"open"). Thus, one basis for classifying membrane channels is the membrane potential necessary to activate (or "gate") them (voltage dependency). For example, "T-type" calcium channels are activated at a lower voltage than L- or N-type channels (Nowycky et al., *Nature*, 316, 440-43 (1985)). Other physiological properties are the activation kinetics, inactivation kinetics, tail current (deactivation kinetics), and single channel conductance. Thus, in comparison to other calcium currents. T-type calcium current is characteristically short (Chen et al., *J. Gen. Physiol.*, 96, 603-30 (1990)), and it exhibits characteristically slow activation kinetics near threshold. fast inactivation kinetics, and slow tail current (Randall et al., *Neuropharmacol.*, 63, 879-93 (1997); Carbone et al., *Nature*, 310, 501-02 (1984); Nilius et al., *Nature*, 316, 443-46 (1985)).

Calcium currents have been implicated in many neurological and muscular functions. For example, T-type calcium current is associated with cardiac pacemaker activity, pain transmission in the central nervous system, and in other physiological functions. Defects in T-type calcium current have been implicated in cardiac arrhythmia, hypertension, and epilepsy. Given their potential clinical value, the pharmacological properties of calcium channels have been the subject of extensive study. Most such studies have involved L-type channels because, unlike T-type channels, L-type calcium channels are readily purified from cell extracts. For example, L-type calcium channels have been purified using dihydropyridine drugs (e.g., nifedipine) which can bind with sufficiently high affinity to serve as a ligand for purifying L-type calcium channels. Such purified and cloned L-type calcium channels have been used to develop assays for drugs affecting L-type calcium channels (see, e.g., U.S. Patents 5,429,921 and 5,386,025).

While many electrophysiological characteristics of T-type calcium currents are known, the lack of isolated T-type channels has stalled research into the pharmacology and biophysics underlying the T-type calcium current, at least in comparison with other calcium channels. Indeed, while it is generally assumed that voltage-sensitive ion channels are responsible for the current, no such channel protein, nor any nucleic acid encoding such a protein, has been isolated. In view of the foregoing problems, there exists a need for an isolated T-type calcium channel and a nucleic acid encoding a T-type calcium channel.

BRIEF SUMMARY OF THE INVENTION

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel and cells and cell lines expressing such nucleic acids. The present invention also provides an isolated or substantially purified T-type calcium channel and an isolated or

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substantially purified antibody molecule recognizing an epitope on a T-type calcium channel protein.

The present invention is useful for exploring the electrophysiology and pharmacology of the T-type calcium current. Such knowledge can lead to the development of drugs for potentiating or attenuating T-type calcium channels. Thus, the present invention provides an assay for identifying potential drugs affecting T-type calcium channels by exposing cells expressing a T-type calcium channel to a putative drug and then measuring the calcium flux in response to a change in membrane potential. The identification of drugs affecting T-type calcium channels will facilitate even greater understanding of the biophysics of these proteins. Furthermore, some such drugs could have potential clinical applications.

The invention can best be understood with reference to the accompanying drawings and in the following detailed description of the preferred embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1E compare the complete amino acid sequences of three types of T-type calcium channels (α 1G (or Ca,T.1), α 1H (or Ca,T.2), and α 1I (or Ca,T.3)), indicating conserved functional domains.

Figures 2A-2D are graphic representations of the current-voltage relationships of three cloned T-type calcium channels (Figures 2A, 2B, and 2C) and a cloned R-type calcium channel (Figure 2D).

Figure 3A is a graphic representation of the average current-voltage curve for cloned T-type calcium channels (α 1G, triangles, α 1H, inverted triangles, α 1I, circles), and a cloned R-type calcium channel (filled squares). Figure 3B compares the normalized conductance of a cloned T-type calcium channel at three different concentrations of BaCl₂.

Figure 4 depicts average kinetics of the tail current as a function of repolarization potential for $\alpha 1G$ (triangles), $\alpha 1H$ (inverted triangles), $\alpha 1I$ (circles), and a cloned R-type calcium channel (filled squares).

Figures 5A and 5B graphically present data concerning the use of a cloned T-type calcium channel to detect drugs affecting the channel. Figure 6A depicts the effect of $100~\mu M$ on current-voltage relationships with a single dosage of miberfradil. Figure 6B illustrates the effect on T-type channel conductance of various doses of miberfradil.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel α

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subunit. The nucleic acid can be of any type, and it can include other elements aside from a sequence encoding a T-type calcium channel domain or domains. For example, where the nucleic acid comprises RNA, it can also include regulatory sequences suitable to permit translation of the RNA. Thus, an RNA nucleic acid of the present invention preferably has at least one ribosome entry site, and preferably has a polyadenosine tail for stabilizing the RNA in the cellular environment. Similarly, DNA nucleic acids of the present invention can have regulatory elements for promoting the transcription of sequence encoding the T-type calcium channel into an RNA such as that described above. For example, a DNA nucleic acid of the present invention can have a promoter and/or an enhancer sequence. While the nucleic acid can be any type of nucleic acid, the nucleic acid preferably comprises a cDNA. A cDNA nucleic acid is preferred over other nucleic acids to permit the nucleic acid to be readily cloned, sequenced, and expressed in a wide variety of cells.

The choice of promoter and/or an enhancer will largely depend on the milieu in which the nucleic acid is to be expressed. Thus, for expression in bacterial cells, the regulatory elements are bacterial promoters. Similarly, for expression in mammalian cells, the regulatory elements are able to effect expression in mammalian cells. While many such regulatory elements are known in the art, examples include prokaryotic promoters and viral promoters (e.g., retroviral ITRs, LTRs, immediate early viral promoters (IEp), such as herpesvirus IEp (e.g., ICP4-IEp and ICP0-IEp), cytomegalovirus (CMV) IEp, and other viral promoters, such as Rous Sarcoma Virus (RSV) promoters, and Murine Leukemia Virus (MLV) promoters). Other suitable promoters are eukaryotic promoters, such as enhancers (e.g., the rabbit β-globin regulatory elements), constitutively active promoters (e.g., the β-actin promoter, etc.), signal specific promoters (e.g., inducible promoters such as a promoter responsive to RU486, etc.), and tissue-specific promoters (e.g., those active in epidermal tissue, dermal tissue, tissue of the digestive organs (e.g., cells of the esophagus, stomach, intestines, colon, etc., or their related glands), smooth muscles, such as vascular smooth muscles, cardiac muscles, skeletal muscles, lung tissue, hepatocytes, lymphocytes, endothelial cells, sclerocytes, kidney cells, glandular cells (e.g., those in the thymus, ovaries, testicles, pancreas, adrenals, pituitary, etc.), tumor cells, cells in connective tissue, cells in the central nervous system (e.g., neurons, neuralgia, etc.), cells in the peripheral nervous system, and other cells of interest).

The isolated or substantially purified nucleic acid of the present invention encodes all or part of a T-type calcium channel α subunit. As used herein, a "calcium channel" includes a protein structure for facilitating the flux of calcium ions across a biological membrane into which the calcium channel is inserted. As used herein, a "T-type channel" is a type of voltage-gated ion channel that facilitates the flux of ions

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when the membrane potential of a biological membrane into which it is inserted experiences a slight depolarization. Thus, a T-type calcium channel can begin to gate from about -60 mV to about -30 mV (i.e., about -45 mV to about -35 mV) in about 10 mM Ba²⁺. Additionally, T-type channels of the present invention exhibit a slow deactivation (tail current) following depolarization. Thus, a T-type calcium channel can exhibit a tail current that decays exponentially with a tau value from about 1 ms to about 10 ms (e.g., from about 4 ms to about 7 ms, such as about 6 ms) following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a Ba²⁺ concentration of from about 10 mM to about 40 mM. Another defining characteristic of T-type calcium channels is that they exhibit small single channel conductance. Thus, for example, a T-type channel exhibits a single channel conductance of from about 4 pS to about 12 pS (e.g., from about 6 pS to about 10 pS), and typically from about 7 pS to about 9 pS in a solution with a Ba²⁺ concentration of about 0.1 M.

The isolated or substantially purified nucleic acid of the present invention encodes all or part of any T-type calcium channel having at least one of the aforementioned electrophysiological properties when properly assembled within a cellular membrane. The general structure of calcium channels is summarized above and is otherwise known in the art. Thus, for example, the nucleic acid can encode one of the four functional domains mentioned above. As used herein, a domain of a Ttype calcium channel is any protein structure able to associate with three other domains to form a tetrameric body functioning as a T-type calcium channel. While the native T-type calcium channel structure includes all four domains in a single polypeptide (indicated in Figures 1A-1E), a domain can exist as a polypeptide species separate from those containing the other domains. Such separate domains are able to associate within the plasma membrane to form a functional channel. Alternatively, where a plurality of domains are linked within a common polypeptide, the linkage can deviate substantially from the native linkage. Thus, for example, the domains can be linked by polypeptide sequences other than those sequences linking the domains in the native protein (e.g., non-native polyglutamate linkages). Indeed, the domains themselves can include non-native linkages between membrane-spanning elements within the domains. Aside from these modifications, the nucleic acid can encode a chimeric calcium channel domain (or an entire channel) comprising a portion of a Ttype calcium channel and a portion derived from another calcium channel (or other channel) protein. For example, the chimera can include portions of domains from Ttype channels responsible for low voltage gating and portions of domains from other calcium channels responsible for slow inactivation. Such a protein exhibiting T-type gating but longer inactivation kinetics would facilitate pharmacological research.

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As mentioned, nucleic acids of the present invention can encode an entire Ttype channel (i.e., a T-type channel protein comprising four functional domains). It has been discovered that at least three genes encoding T-type calcium channels exist in humans and rats (i.e., $\alpha 1G$ (or Ca,T.1), $\alpha 1H$ (or Ca,T.2), and $\alpha 1I$ (or Ca,T.3)), and alternate splicing of these isoforms exist. Examples of the amino acid sequences of full-length T-type channels, and the sequences of suitable coding nucleic acids are set forth at SEQ ID NOs:1-8 (α1G sequences). SEQ IS NOs:9-10 (α1H sequences), and SEQ ID NOs: 11-12 (all sequences). However, the invention is not limited to these exemplary sequences. Indeed, as mentioned, an amino acid sequence of a T-type calcium channel can vary from those listed, and it is within the state of the art to change a nucleotide sequence encoding a T-type channel to introduce mutations into the protein. Indeed, for conducting electrophysiological assays, it may be desirable to introduce mutations into such a protein. For example, mutations comprising insertions or deletions can be introduced on either the amino- or carboxy-terminus of the protein, or such mutations can be intrasequence insertions or deletions. Where the electrophysiological properties of the calcium channel are to be conserved, such mutations preferably are in regions other than the membrane spanning domains. However, in some applications (e.g., to decrease inactivation kinetics), the changes can be within the membrane-spanning regions. Moreover, as mentioned above, the sequence can form a protein having only one functional domain of a T-type calcium channel. Additionally, the sequence can also form a chimeric protein or domain, such as those described above.

Aside from insertions and deletion mutations of native T-type calcium channel sequences. a T-type calcium channel can include substitutions of amino acid residues, e.g., for those indicated in SEQ ID NOs:1-12. Preferably, and especially where such a substitution is within a membrane spanning region, the substitution is conservative. Thus, within membrane spanning domains, positively-charged residues (H, K, and R) preferably are only substituted with positively-charged residues; negatively-charged residues (D and E) preferably are only substituted with negatively-charged residues; neutral polar residues (C, G, N, Q, S, T, and Y) preferably are only substituted with neutral polar residues; and neutral non-polar residues (A, F, I, L, M, P, V, and W) preferably are only substituted with neutral non-polar residues. Preferably, any amino-acid substitution within the membrane-spanning regions does not alter this conservation. Most preferably, any substitution, deletion, or insertion does not alter the IVS4 domain. In each of the exemplary T-type calcium channel α subunit sequences, the putative IVS4 region comprises SEQ ID NO:13. Given the strong sequence conservation among families of voltage-gated ion channels, it is likely that this sequence or a derivative sequence, will be present in T-type channels. Thus, the

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present invention provides any T-type calcium channel (or a nucleic acid encoding such a T-type calcium channel) comprising SEQ ID NO:13 or a sequence derived from SEQ ID NO:13 having conservative amino acid substitutions, as described above.

The nucleic acid of the present invention encoding all or a part of a T-type calcium channel can be isolated via any suitable method. For example, prior to the present invention, one of skill in the art could design a probe based on the sequence of known, non-T-type, calcium channels and use such probe to screen a genetic library. If such a screen were to identify a putative calcium channel, the researcher could then attempt to clone the entire nucleic acid to characterize it. Similarly, prior to the present invention, to isolate a nucleic acid encoding a T-type calcium channel, one of skill in the art could consult publicly available databases containing DNA sequences (e.g., Genbank) to locate nucleic or amino acid sequences representing a portion of a T-type calcium channel protein or nucleic acid. However, such databases contain no sequence for a full-length T-type calcium channel or identify any sequence as a T-type channel. Such methods assume that T-type calcium channels share sufficient sequence identity with known calcium channel nucleic acids to cross-hybridize, an assumption not supported by any published report. Moreover, prior to the present invention, no partial sequence in such databases was identified as corresponding to a T-type calcium channel. Thus, prior to the present invention, the presence of partial sequences in the public DNA databases could facilitate the isolation of T-type calcium channels only with the exercise of a considerable degree of speculation on the part of the researcher.

By providing several sequences pertaining to T-type calcium channels and a comparison presenting conserved regions and domains, the present invention greatly facilitates the isolation of other nucleic acids encoding T-type calcium channels (or derivatives thereof) with much less experimentation. Thus, while any of the methods discussed above can be employed to isolate other members of this genus, preferably, a nucleic acid encoding a T-type calcium channel is isolated by probing a genetic library using a probe that hybridizes to a DNA encoding a peptide sequence contained in (or similar to) a known T-type calcium channel (e.g., SEQ ID NOs:1-12). To facilitate the isolation of a T-type calcium channel, the present invention provides an isolated polynucleotide hybridizing to a portion of the nucleic acid of the present invention encoding a T-type calcium channel (or a portion thereof). Thus, for example, the present invention includes an isolated polynucleotide hybridizing to SEQ ID NO:1-12. The isolated polynucleotide can hybridize to all or any portion of the sequence encoding the T-type calcium channel.

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To isolate such a polynucleotide, any portion of a sequence encoding a T-type calcium channel can be employed as a probe to screen a genetic library, and such screening can be accomplished by standard techniques known in the art. While the probe can hybridize to any portion of such a DNA, preferably the probe is designed to hybridize to a DNA encoding a polypeptide sequence that is highly conserved among T-type calcium channels but is less conserved between the genus of T-type calcium channels and other proteins. Such peptide sequences are readily apparent from the sequence comparison set forth in Figures 1A-1E. Generally, the specificity of hybridization in a genetic screen varies depending on the length of the probe and the stringency (e.g., temperature, salt and detergent concentration, etc.) of hybridization. Stringency of hybridization is broadly classified as "high," "moderate," or "low," and the parameters of these terms are well recognized in the art (see, e.g., Sambrook et al.. "Molecular Cloning, a Laboratory Manual," Cold Spring Harbor Press, 1989). The isolated polynucleotide hybridizing to a portion of the nucleic acid encoding a T-type calcium channel can hybridize under any desired stringency conditions. However, for identifying other T-type channels, preferably, the hybridization occurs under moderate stringency, and most preferably under high stringency.

Of course, the isolated or substantially purified polynucleotide can itself be employed as a probe to screen a library as described to isolate a second nucleic acid. In such a screen, one of the polynucleotides will be complementary to a portion of the sequence encoding the T-type calcium channel, and the other isolated nucleic acid will be "sense." Preferably, one of the two isolated polynucleotides (the "sense" strand) itself encodes a T-type calcium channel, or at least one domain thereof. Such a sequence can be cloned to be operably linked to suitable regulatory elements, as described, to produce a T-type calcium channel. Thus, aside from using the nucleic acid of the present invention to produce a T-type calcium channel, the nucleic acids of the present invention are also useful for isolating other sequences encoding T-type calcium channels, or derivatives thereof.

However isolated, the isolated or substantially purified nucleic acid of the present invention is useful, in part, for producing all or a portion of a T-type calcium channel. Thus, the nucleic acid can be introduced into a suitable milieu for driving its expression. Because T-type channels are transmembrane proteins, preferably such a milieu is a living cell. However, it should be understood that the nucleic acid can also be expressed *in vitro* under conditions, such as those known in the art, suitable for *in vitro* transcription and translation. However produced, the present invention includes any protein, such as a recombinant protein or an isolated or substantially purified protein, including all or a portion of a T-type calcium channel or a protein derived from a T-type calcium channel.

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For expression in a living cell, the nucleic acid must be introduced into the cell. As nucleic acids are generally introduced into cells as part of genetic vectors, the present invention provides a vector having a T-type calcium channel nucleic acid of the type described above. Any type of vector suitable for introducing the nucleic acid into a host cell is within the context of the present invention. Examples of such vectors include naked DNA and RNA vectors (such as oligonucleotides, plasmids, capped cRNA, etc.), viral vectors such as adeno-associated viral vectors (Berns et al., *Annals of the New York Academy of Sciences*, 772, 95-104 (1995)), adenoviral vectors (Bain et al., *Gene Therapy*, 1, S68 (1994)), herpesvirus vectors (Fink et al., *Ann. Rev. Neurosci.*, 19, 265-87 (1996)), packaged amplicons (Federoff et al., *Proc. Nat. Acad. Sci. USA*, 89, 1636-40 (1992)), pappiloma virus vectors, picornavirus vectors, polyoma virus vectors, retroviral vectors, SV40 viral vectors, vaccinia virus vectors, and other vectors. Once a given type of vector is selected, its genome must be manipulated for use as a background vector, after which it must be engineered to incorporate exogenous polynucleotides. Such manipulations are known in the art.

The vectors of the present invention are useful for introducing a nucleic acid encoding all or a portion of a T-type calcium channel into a host cell. Thus, the present invention provides a cell into which the vector of the present invention has been introduced. The host cell can be any cell suitable for expressing the nucleic acid (e.g., bacteria, insect cells, mammalian cells, etc.). The host cell can thus be *in vitro* or *in vivo*. Preferably the cells do not exhibit native T-type calcium current. A preferred cell type is HEK-293 cells because they contain genetic elements that facilitate the expression of transgenes from a variety of expression vectors. For facilitating electrophysiological recordings, oocytes (e.g., *Xenopus* oocytes) are preferred, as they are large and readily handled.

The vector can be introduced into the cell in any manner suitable for the cell type and vector employed. In one embodiment, the vector can be used to prepare an RNA transcript *in vitro* (e.g., a capped cRNA) which is then introduced into the host cell by standard methods (such as injection). Such techniques are preferred when the host cells do not actively transcribe DNA (such as oocytes). In other embodiments, a DNA vector is introduced into the cell such that it is transcribed within the cell. For example, the vector can be introduced into the cell such that it forms an extrachromosomal segment of genetic material in the cell, as is the case with many types of viral vectors. Alternatively, the vector can introduce the nucleic acid into the chromosomal DNA of the host cell.

Preferably, a cell into which the nucleic acid is introduced is also able to express the nucleic acid to produce the α subunit protein. The expression of the nucleic acid can be detected by probing the cell for the presence of T-type calcium

channel mRNA, such as via Northern hybridization analysis, in situ hybridization, etc. More preferably, however, the cell is able to express the nucleic acid to produce the protein including all or a portion of a T-type calcium channel. In such cells, expression of the nucleic acid is confirmed by detecting the protein, for example, by probing cellular extracts with an antibody recognizing the protein (e.g., on a Western blot, etc.).

In the membrane of the cell producing the protein, the expressed protein contributes to the formation of a functional calcium channel. Where the protein encodes an entire α subunit, the full protein will possess some or all of the electrophysiological properties of T-type calcium channels described above. Where the protein encodes less than an entire channel α subunit (e.g., a domain), the protein will aggregate with other constituent domains in the membrane to form a functional channel. Thus, the presence of the protein can be detected by assaying the cell for T-type calcium channel activity. Indeed, assaying for channel activity serves to determine whether a nucleic acid encoding a putative calcium channel, in fact, encodes a species of T-type channel (as opposed to a member of another genus of calcium channels). For example, when large cells (e.g., oocytes) are used as the host cells, the electrophysiological properties of the channel can be investigated. Thus, the membrane activity of whole cells expressing the nucleic acid can be measured directly, such as via patch clamp techniques using a voltage clamp electrode and a current electrode (Bernal et al., J. Pharmacol. Exp. Ther., 282, 172-80 (1997)). Alternatively, the activity of single channels can be measured, such as with a standard depolarizing bath and pipette solutions (Lacerda et al., Biophys. J., 66, 183-43 (1994)). However measured, the properties of cells into which the putative nucleic acid is introduced are compared to the channel conductance, voltage dependency, activation kinetics, inactivation kinetics, or tail current known for T-type channels and discussed above. A measure of current density (e.g., pA/pF) can also be used to assess the level of gene expression in the cells, normalizing for cellular volume.

While, in accordance with the present invention, an isolated cell into which the T-type calcium channel nucleic acid has been introduced (and preferably stably expressing the nucleic acid to produce the protein) can be prepared, preferably, such transfection protocols result in a population consisting essentially of such transfected cells. For standardizing the results of many experiments, it is even more desirable to employ an established cell line consisting essentially of such cells. Preferably, for use in high throughput assays, cell lines stably expressing a T-type calcium channel exhibit a current density of at least about 40 pA/pF (e.g., at least about 45 pA/pF), such as about 50 pA/pF or even 55 pA/pF or higher. Preferably, a cell line in accordance with the present invention is able to propagate the nucleic acid through

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several passages (e.g., for at least 10 passages), and, preferably, the nucleic acid is stably integrated into the chromosomes of such cells. Thus, the cell line can propagate the nucleic acid for at least 20 passages, and more preferably significantly more than 20 passages (e.g., at least about 25 passages, or even more).

Regardless of the cell system, the ability to express a T-type calcium channel nucleic acid within host cells to produce an active channel permits the channel to be further studied. In this regard, the present invention provides a method of identifying a drug which affects T-type calcium channels. The method involves first expressing a T-type calcium channel in a cell to produce an active channel, as herein described. The cell expressing the channel is then exposed to a solution containing a putative drug for interfering with the channel. Thereafter, the presence or absence of calcium flux in response to a change in membrane potential is assayed. Any such assay can be employed within the context of the present invention, (e.g., using labile dyes, radioisotopes (e.g., ⁴⁵Ca), recording electrophysiological changes in the membrane, etc.). A quick method of assaying for calcium flux is first to introduce a calcium-sensitive labile dye into the cells. For example, the dye can be one such as those that fluoresce or change color in the presence of calcium, many of which are known to those of skill in the art (e.g., Indo-1). Thereafter, the cells are exposed to a depolarizing solution containing high (e.g., about 50 mM) potassium concentration and a drug, and the reaction of the labile dye is compared to control cells. Using a labile dye affords the ability to assay many putative drugs quickly in a high throughput assay for putative drugs affecting T-type channels. For example, the initial screening can be carried out in 96 well plates. Moreover, dose-response data can be readily generated by exposing the cells to several concentrations of the same putative drug.

Once a putative drug is detected, its effect on the electrophysiology of the cell (e.g., single channel conductance, voltage dependency, activation kinetics, inactivation kinetics, and tail current of the cells) can be investigated in detail. Generally, the effect of the putative drug on T-type calcium currents is assessed by measuring the various electrophysiological parameters in the presence of various concentrations of the drugs and comparing the data to untreated (or sham-treated) control cells. Cells preferably are maintained in a continuous perfusion chamber during such experiments to facilitate changing solutions. The inventive method of identifying a drug which affects T-type calcium channels can employ any nucleic acid encoding a T-type calcium channel (or derivative thereof), such as those nucleic acids described herein. In fact, as several isoforms of T-type channel exist, the assay method can be repeated using nucleic acids encoding different isoforms to identify

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WO-99/29847 PCT/US98/23161

drugs that preferentially target a given isoform, or drugs which affect more than one isoform of T-type calcium channels.

Aside from affording an in vitro assay for detecting potential therapeutic or investigative drugs targeting T-type calcium channels, the method of expressing the T-type calcium channel nucleic acid can also be used in vivo. For example, as mentioned, several neurological and muscular diseases or disorders have implicated mutations affecting native nucleic acids encoding T-type calcium channels. The present invention, thus, provides a method of treating a disease or disorder associated with a deficiency in a native T-type calcium channel nucleic acid. The method involves introducing a vector having the T-type calcium channel nucleic acid into cells of a host in which native expression of the nucleic acid is deficient. Thus, for example. for treating cardiomyopathy associated with deficiencies in T-type calcium channels, the vector is introduced into myocardial cells. Similarly, for treating forms of epilepsy associated with deficiencies in T-type calcium channels, the vector is introduced into neurons (e.g., thalamic neurons). Within the target cells, the nucleic acid within the vector is expressed to produce active T-type calcium channel. By similar methods, an nucleic acid having a sequence antisense to a sequence encoding a T-type calcium channel (or a portion thereof) can be expressed within a cell. The presence of an antisense sequence can down-regulate the expression of native T-type calcium channel genes by hybridizing to T-type channel mRNA within the cell. Thus, the present invention is useful to treating disorders associated with over-expression of T-type calcium channels.

T-type channel proteins (such as whole T-type calcium channels, domains of such channels, chimeras including portions of T-type calcium channels, etc.) can be employed to generate antibodies (e.g., immunoglobulins) to T-type calcium channels. Thus, the present invention provides an isolated and substantially purified antibody molecule recognizing an epitope on a T-type calcium channel. Such antibodies can be monoclonal antibodies or polyclonal antisera. Antibodies recognizing T-type calcium channels can be used to purify the channels from cell extracts or other solutions by standard methodologies (e.g., immunoprecipitation). Moreover, depending on the location of the epitopes for the antibodies on the T-type calcium channel, the antibodies can be used to affect the channel proteins present on the surface of cells. Thus, antibodies directed to T-type calcium channels are potential reagents for studying the channels as well as for therapy.

Such antibodies can be produced by any suitable method, many of which are well known in the art. Thus, for example, the antibodies can comprise polyclonal antisera obtained from innoculated animals. Alternatively, the antibody molecules can be monoclonal antibodies obtained from a cell line (e.g., a hybridoma cell line). Thus,

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the present invention provides a cell which produces such antibodies. Such a cell can be *in vitro* or *in vivo*; however, where the cell is *in vitro*, preferably it is within an established cell line consisting essentially of such cells.

Several examples are presented below to illustrate the invention. Taken together, the examples demonstrate the cloning of twelve novel proteins and their characterization as T-type calcium channel α subunits. These examples are included here for purely illustrative purposes; as such, they are not to be construed so as to limit the scope of any aspect of the invention.

Many procedures employed in the following examples are techniques routinely performed by one of ordinary skill in the art (see generally Sambrook et al., *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory. Cold Spring Harbor, NY (1989)) and are not discussed in detail. However, some reagents and methods deserve specific description. Thus, for example, in vitro translation and expression were conducted as described previously (Schneider et al., *Receptors and Channels*, 2, 255-70 (1995)). *Xenopus laevis* oocytes were prepared as described previously (Bernal et al., *J. Pharmacol. Exp. Ther.*, 282, 172-80 (1997)). To express proteins, 10 or 30 ng of capped cRNA was injected into the oocytes in a volume of 50 nl. For single channel recording, oocytes were injected with 100 ng capped cRNA and incubated for one week prior to assay.

Cells were voltage clamped using a two-microelectrode voltage clamp amplifier as described (Bernal et al., *J. Pharmacol. Exp. Ther.*, 282, 172-80 (1997)). The standard bath solution contained the following: 40 mM Ba(OH)₂, 50 mM NaOH, 1 mM KOH, 0.1 mM EDTA, and 5 mM HEPES, adjusted to pH 7.4 with methanesulfonate. The osmolality of the 2 mM Ba²⁺ and 10 mM Ba²⁺ solutions was balanced by increasing the NaOH concentration as described (Lory et al., *J. Physiol.*, (London), 429, 95-112 (1990)). Voltage and current electrodes (1.5-1.8 M tip resistance) were filled with 3 M KCl. Except as noted, data were acquired at 4 kHz using the pCLAMP system, and filtered at 1 kHz. Data were analyzed using pCLAMP software. Boltzman fits and linear regression were calculated using Prism.

EXAMPLE 1

This example demonstrates the cloning and characterization of putative T-type calcium channels.

A search of the Genbank library was conducted to identify clones identified as having some degree of homology to known calcium channel sequences. The search identified an expressed sequence tagged (EST) partial sequence in a human brain clone (H06096), which was used as a probe to screen a \(\lambda gt10 \) cDNA library prepared

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from rat brain. Successive screening of the cDNA library identified five overlapping clones which were aligned to construct an entire cDNA sequence, termed $\alpha 1G$.

The αIG cDNA was cloned into the pSP72TM vector and sequenced by standard computer-assisted sequencing. Using the alG cDNA, the amino acid 5 sequence of the $\alpha 1G$ protein was deduced and compared to the sequences of other known calcium channel a subunits. By similar methods, homologous human (H19230 and R19524) and mouse (AA286626) EST clones were also identified and partially sequenced, and alternately spliced variants were identified. The deduced cDNA and amino acid sequences for eight full-length $\alpha 1G$ T-type channels are set forth, respectively, as SEQ ID NOs:1-8.

A second T-type calcium channel, termed alH, was isolated by screening a human heart cDNA library with a fragment of the α1G sequence. An alternately spliced isoform was also identified. The full-length cDNA and amino acid sequences for these α1H T-type channels are set forth, respectively, as SEQ ID NOs:9 and 10.

A third T-type calcium channel, termed αH , was isolated by screening a rat brain cDNA library at low stringency using a fragment of the rat a1G gene. Fifty plaques were identified, many of which were not detected in a second screening. A third screening with a fragment from a1H identified two clones. Subsequent screening, and the use of the GenBank database, led to the identification of the full. length rat and human cDNA and amino acid sequences, set forth at SEQ ID NOs: 11 and 12, respectively.

The α 1G, α 1H, and α 1I amino acid sequences were compared to each other and a known calcium channel ($\alpha 1E$) to investigate the conservation of protein structure and function. The comparison indicates that the $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ amino acid sequences within the putative membrane-spanning domains are about 90 %identical to each other, while the $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ sequences are only roughly 40 % identical to the α IE clone.

Figures 1A-1E indicate this conservation between the proteins. The conservation of charged residues, particularly in the S4 domains, is consistent with the role of the α1G, α1H, and α1I proteins as ion channels. However, two of the glutamates associated with ion specificity in other calcium channels have been replaced with aspartate, suggesting altered ion selectivity. Strikingly, a1G, a1H, and all display only low homology to sequences linking the membrane-spanning regions within each domain, and even less homology between the intracellular loops linking domains. Notably, neither $\alpha 1G$, $\alpha 1H$, nor $\alpha 1I$ possesses sequences known to bind β subunits or Ca²⁺ ions.

EXAMPLE 2

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This example demonstrates the production of cell lines stably expressing the cloned α1G. α1H. and α1I proteins.

HEK-293 cells were transfected with either the rat α1G cDNA (SEQ ID NO:1). the human $\alpha 1H$ cDNA (SEQ ID NO:9), or the rat $\alpha 1I$ cDNA (SEQ ID NO:11). As a control, cells were also transfected with human $\alpha 1E$ plus human $\beta 3$ (Schneider et al., Receptors Channels, 2, 255-70 (1994); Murakami et al., Eur. J. Biochem., 236, 138-43 (1996)). The DNA constructs included a neomycin resistance gene conferring resistance to G418. The cells were cultured under standard conditions using medium containing G418 to select for stable transformants.

Surviving clones were expanded and assayed for electrophysiological activity to determine the presence of channels within the membrane. Whole-cell currents were recorded from ruptured patches using an Axopatch 200A amplifier, Digidata 1200 A/D converter, and pCLAMP 6.0 software. Data were digitized at 2 kHz and filtered at 1 kHz or off-line. All experiments were performed at room temperature. Pipettes 15 were made out of TW-150-6 capillary tubing (World Precision Instruments. Inc., Sarasota, FL), using a Model P-97 Flaming-Brown pipette puller (Sutter Instrument Co., Novato, CA). The internal pipette solution contained the following: 55 mM CsCl, 75 mM CsSO₄, 10 mM MgCl₂, 0.1 mM EGTA, 10 mM HEPES, pH adjusted to 7.2 with CsOH. The external Tyrodes solution was the following: 140 mM NaCl, 6 20 mM KCl, 2 mM CaCl₂, 10 mM glucose, 5 mM HEPES, pH 7.4. The recording solution contained the following: 10 mM BaCl₂ solution (or 2 mM CaCl₂), 140 mM tetraethylammonium (TEA) chloride, 5 mM CsCl. 1 mM MgCl₂, 5 mM glucose, and 10 mM HEPES, pH adjusted to 7.4 with TEA-OH. Under these solution conditions the pipette resistance was typically 1.5-2.5 $M\Omega$. Cell capacitance was measured by integrating the charging current during a 10 mV hyperpolarizing pulse (holding potential -80 mV).

Using these recording techniques, values for pA/pF were obtained for each cell line, which is a measure of current density normalizing for cell size. One clone (#N2) expressed the rat a1G protein and has a current density of 42 pA/pF. Another clone (#13), expressed the human α1H protein and exhibited a current density of 53 pA/pF. Three clones (#11, #19, and #25) expressed the rat $\alpha 11$ protein and exhibited current densities of 40 pA/pF, 45 pA/pF, and 55 pA/pF, respectively

35 EXAMPLE 3

This example demonstrates that the cloned putative T-type calcium channels exhibit T-type current-voltage relationships.

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Current traces were elicited by depolarizing voltage clamp pulses of the membranes of cells. The $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins were produced in *Xenopus laevis* oocytes by linearizing the DNA vectors containing the coding sequences, and transcribing the coding sequences *in vitro* by standard methods. Oocytes were then injected with the capped RNA.

Figures 2A-2E depict data obtained from these experiments using cells injected with $\alpha 1G$ (Figure 2A), $\alpha 1H$ (Figure 2B), and $\alpha 1I$ (Figure 2C) and $\alpha 1E$ (Figure 2D). These data indicate that cells expressing $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ exhibit T-type calcium current, while oocytes expressing $\alpha 1E$ as well as uninjected oocytes (Figure 6A) do not.

Current voltage curves were developed using cells injected with $\alpha 1G$, $\alpha 1H$, $\alpha 1I$, and $\alpha 1E$. Figures 3A depicts such data generated in a 10 mM Ba²⁺ test solution. These data were transformed into conductance and fit with a Boltzman equation to determine the midpoint of activation ($V_{0.5}$). Gating potentials for $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ (-38 ± 1 mV n=8, -44 mV ± 1 mV, n=10, and -31 mV ± 1 mV, n=6, respectively) were in accordance with the gating potential measured for the HEK-293 cells (-41 ± 1 mV, n=10), while $\alpha 1E$ required significantly more positive potentials to open (-2.6 mV ± .4 mV, n=3).

To compare the characteristics with published values (Huguenard, Ann. Rev. Physiol., 58, 329-48 (1996)), the α 1G current was recorded at varying concentrations of Ba²⁺. As indicated in Figure 3B, in solutions containing 2 mM Ba²⁺, V_{0.5} was -46.5 mV, and the slope factor (k) was 6.6 (n=7). However, when the Ba²⁺ concentration was 40 mM, V_{0.5} was recorded at -21 mV, presumably due to the results of barium on surface charge screening (see, e.g., Wilson et al., J. Membrane Biol., 72, 117-30 (1983)). Similar values were recorded for α 1H and α 1I.

These results indicate that $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ are low-voltage activated calcium channels (i.e., from about -60 mV to about -30 mV in 10 mM Ba²⁺).

EXAMPLE 4

This example demonstrates that the cloned putative T-type calcium channels exhibit T-type tail current.

Tail current was measured at -90 mV after first opening the channels with a voltage step to -10 mV. The voltage-dependence of tail current in cells expressing $\alpha 1G$ (oocytes) $\alpha 1H$ (HEK 293 cells), and $\alpha 1I$ (HEK 293 cells) was measured at varying test potentials. As a control, tail current was also measured from a high voltage activated channel $\alpha 1E$, which Raw data from recordings data were fit with a single exponential and plotted as a function of depolarization potential (Figure 4).

These results demonstrate that the tail currents for the cloned $\alpha 1G$. $\alpha 1H$. and $\alpha 1I$ calcium channels are voltage-dependent, consistent with known T-type calcium tail currents. Additionally, these data demonstrate that the tail current for each of the cloned channels is between about 1 ms and about 10 ms following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a barium concentration of from about 10 mM to about 40 mM.

EXAMPLE 5

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This example demonstrates that the cloned putative T-type calcium channels exhibit T-type single channel conductance.

Measurement of single channel conductance is complicated by the low probability of channel opening at negative potentials when the driving force is large. Thus, single channel conductance was measured similarly for measurements of tail currents to enhance channel opening at negative potentials. Single channels were measured with standard depolarizing bath and pipette (115 mM BaCl₂, 1 mM EGTA, and 10 mM HEPES, pH 7.4) solutions (Lacerda et al., *Biophys. J.*, 66, 1833-43 (1994)). Data were analyzed with TRANSIT (VanDongan, *Biophys J.*, 70, 1303-15 (1996)). Single channel amplitudes were measured by averaging the values obtained from Gaussian fits to all-points histograms of traces with openings, selected openings, or amplitude histograms of idealized openings. It has been reported that some oocytes contain a native 9 pS channel. These endogenous channels can be distinguished by their 2-fold larger current amplitudes at the potentials tested (e.g., -20 mV, i = 0.8 for endogenous channels as opposed to 0.4 pA for α 1G). However, such endogenous channels were not detected either at the whole cell or single channel level in the oocytes tested.

Current through the main open state of each open channel was measured at each potential and plotted against each test potential. Single channel currents for several patches were then averaged and plotted as a function of test potential, wherein the slope of the plot indicated the single channel conductance. The average slope conductance of the $\alpha 1G$ channel was measured at 7.5 ± 1.5 pS, which corresponds with the reported values for T-type calcium channels (Hugenard, *Ann. Rev. Phsysiol.*, 58, 329-48 (1996)). Similar results were also obtained with both $\alpha 1H$ (10.8 \pm 1.4 pS). Data collected from recordings of the $\alpha 1I$ channels indicate that they open to two distinct amplitudes, The conductance for the small amplitude $\alpha 1I$ openings was measured at 3.9 ± 0.5 pS, while that for the large $\alpha 1I$ openings was measured at 11.4 ± 0.5 pS).

These results indicate that the cloned $\alpha 1G$, $\alpha 1H$, and $\alpha 1I$ proteins exhibit T-type single-channel conductance (e.g., from about 4 to about 12 pS).

EXAMPLE 6

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This example demonstrates that a cloned T-type calcium channel can be used for identifying a drug which affects T-type calcium channels.

HEK-293 cells were subjected to treatment as indicated above in Example 3, except that an experimental group of cells were exposed to a solution containing 1 μ M mibefradil. a known inhibitor of T-type calcium current. As depicted in Figure 5A, the presence of mibefradil almost completely abolished T-type current in cells expressing $\alpha 1G$. Cells expressing either $\alpha 1G$ or $\alpha 1H$ were similarly treated using various concentrations of mibefradil to determine a dose-response relationship. These results, depicted in Figure 5B, demonstrate that about 50% inhibition was achieved at a mibefradil concentration of 1 μ M.

All of the references cited herein, including patents, patent applications, and publications, are hereby incorporated in their entireties by reference.

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations of the preferred embodiments may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

What is claimed is:

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- 1. A isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel α subunit.
- 2. The nucleic acid of claim 1. wherein said protein comprises an entire T-type calcium channel α subunit.
- 3. The nucleic acid of claim 2, wherein said protein comprises SEQ ID NO:13.
- 4. The nucleic acid of any of claims 1-3, wherein said calcium channel begins to gate from about -60 mV to about -30 mV in 2 mM Ba²⁺.
- 5. The nucleic acid of any of claims 1-4, wherein said calcium channel exhibits a tail current of from about 1 ms to about 10 ms following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a barium concentration of from about 10 mM to about 40 mM.
- 6. The nucleic acid of any of claims 1-5, wherein said calcium channel exhibits a single channel conductance of from about 4 pS to about 11 pS in a solution with a barium ion concentration of about 100 mM.
 - 7. An isolated or substantially purified nucleic acid hybridizing to the nucleic acid of any of claims 1-6.
 - 8. An isolated or substantially purified nucleic acid hybridizing to the nucleic acid of claim 7.
 - 9. The nucleic acid of claim 8 comprising a sequence encoding at least one domain of a T-type calcium channel α subunit.
 - 10. A vector comprising the nucleic acid of any of claims 1-9.
 - 11. A cell into which the vector of claim 10 has been introduced.
 - 12. The cell of claim 11, which expresses said nucleic acid to produce said protein.
 - 13. The cell of claim 11 or 12, which stably expresses said nucleic acid to produce said protein.
 - 14. A population of cells consisting essentially of cells according to any of claims 11-13.
 - 15. An established cell line consisting essentially of cells according to any of claims 11-13.
- 16. A method of identifying a drug which affects T-type calcium channels, said method comprising expressing a T-type calcium channel in a cell, exposing said cell to a putative drug, and measuring the calcium flux through the membrane of said cell in response to a change in membrane potential.

- 17. The method of claim 16, wherein said calcium flux is assayed by using a calcium-sensitive labile dye within said cell.
- 18. The method of claim 16, wherein said calcium flux is assayed by measuring the electrophysiological properties of said cell.
- 19. The method of claim 16. wherein said calcium channel comprises SEQ ID NO:13.
- 20. An isolated or substantially purified immunoglobulin recognizing an epitope on a T-type calcium channel protein.
 - 21. A cell in vitro which produces the immunoglobulin of claim 20.
- 22. An established cell line consisting essentially of cells according to claim 21.

----SFTQLNDLSGAGGRQGPGSTEKDPGSADSEAEGLPYPALAPVVFFYLSQDSRPRSWCLRTVCNPW hCavt2a Mtegaraadevrvplgrrpwpcgvgggvpgeprgagtrggggfelgvspsespaaercaelgadeeorvpypalaatvffclgottrprswclrlvcnpw ----APEPG--ITEQPGPRSPPPSPPGLEEPLEGINPDVPHPDLAPVAFFCLRQTISPRNWCIKMYCNPW ----SFMRINDLSGAGGRPGPGSAEKDPGSADSEAEGLPYPALAPVVFFYLSQDSRPRSWCLRTVCNPW ----PAAEPGVTTEQPGPRSPPSSPPGLEEPLDGADPHVPHPDLAPIAFFCLRQTTSPRNWCIKMVCNPW hCavTla MDEEEDGAGAEESGQPR-rCavTla MDEEEDGAGAEESGQPR-MADSNLPPSSAAAP----MAESASPPSSSAAA--hCavT3 rCavT3

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rcavīla llingsffminlcinviatgfsetkoresqlmreqrvrflsnastlasfsepgscyeellkyluyilrkaarrlaqusraigvragllsspvarsgoep hCavT2a LLIIVGSFFMINLCLVVIATQFSETKQRESQLMREQRARHLSNDSTLASFSEPGSCYEELLKYVGHIFRKVKRRSLRLYARWQSRWRKKVDPSAVQGQGP hcavtla iliivgsffminicivviatofsetkoresqimreqrvftsnastlasfsepgscyeelikyivyilrkaarriaqvsraagvrvgilsspapiggoet hCavT3 LLIIVGSFFMINLCLVVIATQFSETKQREHRLMLEQRQRYLSS-STVASYAEPGDCYEEIFQYVCHILRKAKRRALGLYQALQSRRQ--------LLIIVGSFFMINLCLVVIATOFSETKOREHRIMLEORORYLSS-STVASYAEPGDCYEEIFOYVCHILRKAKRRALGLYQALONRRO---------rCavT3

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hCavIla LOROLVVIMKTMDNVATFCMLIMLFIFIFSILGMHLFGCKFASERD-GDTLPDRKNFDSLLWAIVTVFQILTQEDWNKVLYNGMASTSSWAALYFIALMT rcavīla lorolivilmkīmdnvaffcmlimleifiesilcmhlfgckfaserd-gdīlfdrknfdslimaivīvfgiltoedmnkvlyncmastsswaalyfialmī

IISS

IIP LOOP

LRRQLVVIMKTMDNVATECMLIMLFIFIFSILGMHIFGCKFSLRTDTGDTVPDRKNFDSLLWAIVTVFQILTQEDWNVVLYNGMASTSPWASLYFVALMT LRRQLVVIMKTMDNVATFCMLIMLFIFIFSILGMHIFGCKFSLRTDTGDTVPDRKNFDSLLWAIVTVFQILTQEDWNVVLYNGMASTTFWASLYFVALMT

hCavT3

rCavT3

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hCavT1a

hCavT3 rCavT3

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hCavT3

rCavT3

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hCa,Tla SYM rCa,Tla SYM hCa,T2a SYM hCa,T3 rCa,T3	hCa,Tla DLL rCa,Tla DLL hCa,T2a hCa,T3	hCa,Tla AQS' rCa,Tla TQS'	hCa,Tla SMA, rCa,Tla STA		:

Fig. 1E

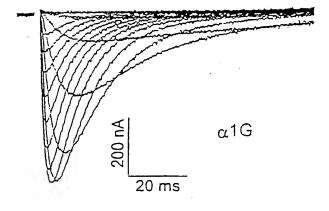


Figure 2A

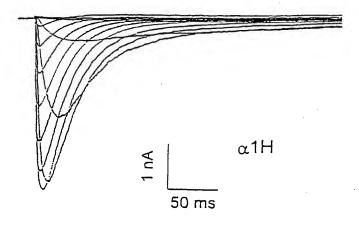


Figure 2B

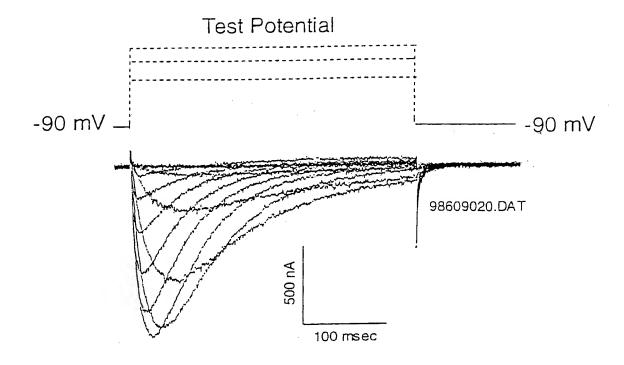


Figure 2C

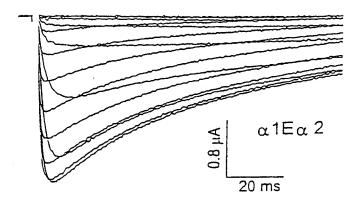


Figure 2D

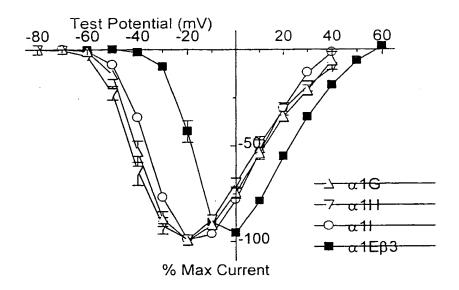


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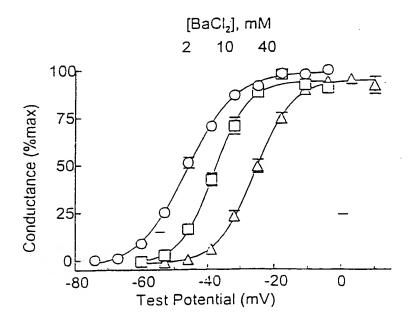


Figure 3B

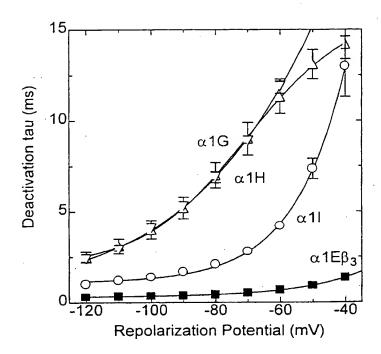


Figure 4

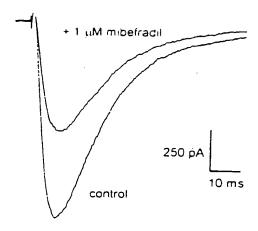


Figure 5A

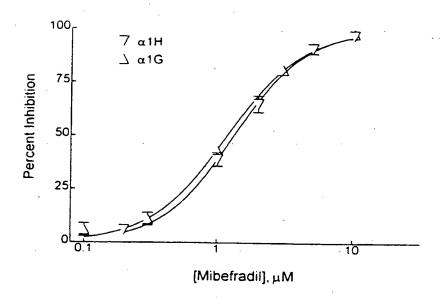


Figure 5B

SEQUENCE LISTING

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	<140> <141>															. •
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	cgg aç Arg Se	gc ttc er Phe	atg Met 20	cgg Arg	ctc Leu	aac Asn	gac Asp	ctg Leu 25	tcg Ser	ggg ggg	gcc Ala	ggg Gly	999 Gly 30	cgg Arg	ccg Pro	96
40	ggg co Gly Pr	eg ggg co Gly 35	tca Ser	gca Ala	gaa Glu	aag Lys	gac Asp 40	ccg Pro	ggc Gly	agc Ser	gcg Ala	gac Asp 45	tcc Ser	gag Glu	gcg Ala	144
45	gag gg Glu Gl	gg ctg Ly Leu 50	ccg Pro	tac Tyr	ccg Pro	gcg Ala 55	ctg Leu	gcc Ala	ccg Pro	gtg Val	gtt Val 60	ttc Phe	ttc Phe	tac Tyr	ttg Leu	192
50	agc ca Ser Gl 65	ng gac .n Asp	agc Ser	cgc Arg	ccg Pro 70	cgg Arg	agc Ser	tgg Trp	tgt Cys	ctc Leu 75	cgc Arg	acg Thr	gtc Val	tgt Cys	aac Asn 80	240
55	ccc tg Pro Tr	g ttt p Phe	gag Glu	cgc Arg 85	atc Ile	agc Ser	atg Met	ttg Leu	gtc Val 90	atc Ile	ctt Leu	ctc Leu	aac Asn	tgc Cys 95	gtg Val	288
	acc ct Thr Le	g ggc u Gly	atg Met 100	ttc Phe	cgg Arg	cca Pro	tgc Cys	gag Glu 105	gac Asp	atc Ile	gcc Ala	tgt Cys	gac Asp 110	tcc Ser	cag Gln	336
60	ege tg Arg Cy	gc cgg 's Arg 115	atc Ile	ctg Leu	cag Gln	gcc Ala	ttt Phe 120	gat Asp	gac Asp	ttc Phe	atc Ile	ttt Phe 125	gcc Ala	ttc Phe	ttt Phe	384
	gcc gt	g gag	atg	gtg	gtg	aag	atg	gtg	gcc	ttg	ggc	atc	ttt	ggg	aaa	432

	Ala	Val 130	Glu	Met	Val	Va:	Lys 135	Met	Val	Ala	Leu	Gly 140	Ile	Phe	Gly	Lys	
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50	acc Thr	aac Asn	tgc Cys	tca Ser	gcg Ala 325	G] À Gàà	gag Glu	cac His	aac Asn	ccc Pro 330	ttc Phe	aag Lys	ggc Gly	gcc Ala	atc Ile 335	aac Asn	1008
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	ctg Leu	gag Glu	ggc Gly 355	tgg Trp	gtc Val	gac Asp	atc Ile	atg Met 360	tac Tyr	ttt Phe	gtg Val	atg Met	gat Asp 365	gct Ala	cat His	tcc Ser	1104
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13															ggg Gly		. 1392
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	Gly	Asp	Thr	1 Let 900	ı Pro	Asp	Arg	ı Lys	905	n Phe	Ası	o Sei	Let	1 Le: 91		o Ala	ı	
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10	ctc Leu	taç Tyr 930	Asn	ggt Gly	atg Met	gcc Ala	stcc Ser 935	Thr	tcg Ser	tcc Ser	tgo Trp	g gcg Ala 940	Ala	ctt Lei	tat ı Tyr	ttc Phe	:	2332
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20	gaa Glu	tca Ser	gag Glu	ccc Pro 980	gat Asp	ttc Phe	ttc Phe	tca Ser	ccc Pro 985	agc Ser	ctg	gat Asp	ggt Gly	gat Asp 990	Gly	gac Asp		2976
25	agg Arg	aag Lys	aag Lys 995	tgc Cys	ttg Leu	gcc Ala	Leu	gtg Val 1000	tcc Ser	ctg Leu	gga Gly	Glu	cac His 1005	ccg Pro	gag Glu	ctg Leu		3024
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<i>35</i>	atg Met 1025	ser	ctg Leu	ccc Pro	ьys	agc Ser 1030	acc Thr	agc Ser	acg Thr	Gly	ctg Leu 1035	ggc Gly	gag Glu	gcg Ala	Leu	ggc Gly 1040		3120
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	gac .	aca	ctg	cag	gtg	cca	ggg	ctg	cat	cgc	act	gcc	agt	ggc	cga	ggg		3504

	Asp Th	r Leu 1155	Gln	Val	Pro	Gly	Leu 1160	His	Arg	Thr		Ser 1165	Gly	Arg	Gly	
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	ctg gat Leu Asp	gct Ala 1475	gtg Val	ggc Gly	gtg Val	Asp	cag Gln 1480	cag Gln	ccc Pro	atc Ile	Met	aac Asn 1485	cac His	aac Asn	ccc Pro	4464
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	Ala S∈ 1665	r Leu	Pro	Ile	Asn 1670	.Pro	Thr	Ile		Arg 1675		Met	Arg	Val	Leu 1680	
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	ccc aat	gac	agc	tac	atg	tgt	cgg	cat	ggg	agc ·	act	åсс	gag	ggg	ccc	5808

	Pro Asn Asp Ser Tyr Met Cys Arg His Gly Ser Thr Ala Glu Gly Pro 1925 1930 1935	
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<i>30</i> .	too cog coo ctg goo cgg goo tao tot tto tgg ggo cag toa agt aco Ser Pro Pro Leu Ala Arg Ala Tyr Ser Phe Trp Gly Gln Ser Ser Thr 2035 2040 2045	6144
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	<220 <221 <222	> CE		(6783	3)												
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45	gag Glu	999 Gly 50	ctg Leu	ccg Pro	tac Tyr	ccg Pro	gcg Ala 55	ctg Leu	gcc Ala	ccg Pro	gtg Val	gtt Val 60	ttc Phe	ttc Phe	tac Tyr	ttg Leu	192
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	gcc Ala	gtg Val	gag Glu	atg Met	gtg Val	gtg Val	aag Lys	atg Met	gtg Val	gcc Ala	ttg Leu	ggc Gly	atc Ile	ttt Phe	ggg Gly	aaa Lys	432

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	cgc Arg	tat Tyr	tac Tyr	cag Gln 260	aca Thr	gag Glu	aac Asn	gag Glu	gat Asp 265	gag Glu	agc Ser	ccc Pro	ttc Phe	atc Ile 270	tgc Cys	tcc Ser	816
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40	cgc Arg	ggg Gly 290	gac Asp	ggg Gly	ggc Gly	ggt Gly	ggc Gly 295	cca Pro	cct Pro	tgc Cys	ggt Gly	ctg Leu 300	gac Asp	tat Tyr	gag Glu	gcc Ala	912
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	ttc Phe	atg Met	atc Ile	aac Asn	ctg Leu	tgc Cys	ctg Leu	gtg Val	gtg Val	att Ile	gcc Ala	acg Thr	cag Gln	ttc Phe	tca Ser	gag Glu	1200

	385					390					395					400	
5	acc Thr	aag Lys	cag Gln	Arg egg	gaa Glu 405	agc Ser	cag Gln	ctg Leu	atg Met	cgg Arg 410	gag Glu	cag Gln	cgt Arg	gtg Val	cgg Arg 415	ttc Phe	1248
10	ctg Leu	tcc Ser	Asn	gcc Ala 420	agc Ser	acc Thr	ctg Leu	gct Ala	agc Ser 425	ttc Phe	tct Ser	gag Glu	ccc Pro	ggc Gly 430	agc Ser	tgc Cys	1296
	tat Tyr	gag Glu	gag Glu 435	ctg Leu	ctc Leu	aag Lys	tac Tyr	ctg Leu 440	gtg Val	tac Tyr	atc Ile	ctt Leu	cgt Arg 445	aag Lys	gca Ala	gcc Ala	1344
15	cgc Arg	agg Arg 450	ctg Leu	gct Ala	cag Gln	gtc Val	tct Ser 455	cgg Arg	gca Ala	gca Ala	ggt Gly	gtg Val 460	cgg Arg	gtt Val	Gly ggg	ctg Leu	1392
20	ctc Leu 465	agc Ser	agc Ser	cca Pro	gca Ala	ccc Pro 470	ctc Leu	Gly	ggc Gly	cag Gln	gaģ Glu 475	acc Thr	cag Gln	ccc Pro	agc Ser	agc Ser 480	1440
25	agc Ser	tgc Cys	tct Ser	cgc Arg	tcc Ser 485	cac His	cgc Arg	cgc Arg	cta Leu	tcc Ser 490	gtc Val	cac His	cac His	ctg Leu	gtg Val 495	cac His	1,488
<i>30</i>	cac His	cac His	cac His	cac His 500	cat His	cac His	cac His	cac His	tac Tyr 505	cac His	ctg Leu	ggc Gly	aat Asn	ggg Gly 510	acg Thr	ctc Leu	1536
	agg Arg	gcc Ala	ccc Pro 515	cgg Arg	gcc Ala	agc Ser	ccg Pro	gag Glu 520	atc Ile	cag Gln	gac Asp	agg Arg	gat Asp 525	gcc Ala	aat Asn	ggg Gly	1584
35	tcc Ser	cgc Arg 530	cgg Arg	ctc Leu	atg Met	ctg Leu	cca Pro 535	cca Pro	ccc Pro	tcg Ser	acg Thr	cct Pro 540	gcc Ala	ctc Leu	tcc Ser	G] À āāā	1632
40	gcc Ala 545	ccc Pro	cct Pro	ggt Gly	ggc Gly	gca Ala 550	gag Glu	tct Ser	gtg Val	cac His	agc Ser 555	ttc Phe	tac Tyr	cat His	gcc Ala	gac Asp 560	1680
45	tgc Cys	cac His	tta Leu	Glu	cca Pro 565	gtc Val	cgc Arg	tgc Cys	cag Gln	gcg Ala 570	ccc Pro	cct Pro	ccc Pro	agg Arg	tcc Ser 575	cca Pro	1728
50	tct Ser	gag Glu	gca Ala	tcc Ser 580	ggc Gly	agg Arg	act Thr	gtg Val	ggc Gly 585	agc Ser	ggg Gly	aag Lys	gtg Val	tat Tyr 590	ccc Pro	acc Thr	1776
	gtg Val	cac His	acc Thr 595	agc Ser	cct Pro	cca Pro	ccg Pro	gag Glu 600	acg Thr	ctg Leu	aag Lys	gag Glu	aag Lys 605	gca Ala	cta Leu	gta Val	1824
<i>55</i>	gag Glu	gtg Val 610	gct Ala	gcc Ala	agc Ser	tct Ser	ggg Gly 615	ccc, Pro	cca Pro	acc Thr	ctc Leu	acc Thr 620	agc Ser	ctc Leu	aac Asn	atc Ile	1872
60	cca Pro 625	ccc Pro	ggg Gly	ccc Pro	tac Tyr	agc Ser 630	tcc Ser	atg Met	cac His	aag Lys	ctg Leu 635	ctg Leu	gag Glu	aca Thr	ca`g Gln	agt Ser 640	1920
	aca Thr	ggt Gly	gcc Ala	tgc Cys	caa Gln	agc Ser	tct Ser	tgc Cys	aag Lys	atc Ile	tcc Ser	agc Ser	cct Pro	tgc Cys	ttg Leu	aaa Lys	1968 .

					645					650					655		
5	gca Ala	gac Asp	agt Ser	gga Gly 660	gcc Ala	tgt Cys	ggt Gly	cca Pro	gac Asp 665	age Ser	tgc Cys	ccc Pro	tac Tyr	tgt Cys 670	gcc Ala	cgg Arg	201.6
10	gcc Ala	ggg Gly	gca Ala 675	ggg Gly	gag Glu	gtg Val	gag Glu	ctc Leu 680	gcc Ala	gac Asp	cgt Arg	gaa Glu	atg Met 685	cct Pro	gac Asp	tca Ser	2064.
10	gac Asp	agc Ser 690	gag Glu	gca Ala	gtt Val	tat Tyr	gag Glu 695	ttc Phe	aca Thr	cag Gln	gat Asp	gcc Ala 700	cag Gln	cac His	agc Ser	gac . Asp	2112
15	ctc Leu 705	cgg Arg	gac Asp	ccc Pro	cac His	agc Ser 710	cgg Arg	cgg Arg	caa Gln	cgg Arg	agc Ser 715	ctg Leu	ggc Gly	cca Pro	gat Asp	gca Ala 720	2160
20	gag Glu	ccc Pro	agc Ser	tct Ser	gtg Val 725	ctg Leu	gcc Ala	ttc Phe	tgg Trp	agg Arg 730	cta Leu	atc Ile	tgt Cys	gac Asp	acc Thr 735	ttc Phe	2208
25		aag Lys															2256
30	atc Ile	ctg Leu	gtc Val 755	aac Asn	aca Thr	ctc Leu	agc Ser	atg Met 760	ggc Gly	atc Ile	gaa Glu	tac Tyr	cac His 765	gag Glu	cag Gln	ccc Pro	2304
	gag Glu	gag Glu 770	ctt Leu	acc Thr	aac Asn	gcc Ala	cta Leu 775	gaa Glu	atc Ile	agc Ser	aac Asn	atc Ile 780	gtc Val	ttc Phe	acc Thr	agc Ser	2352
35		ttt Phe															2400
40	ggc Gly	tac Tyr	atc Ile	aag Lys	aat Asn 805	ccc Pro	tac Tyr	aac Asn	atc Ile	ttc Phe 810	gat Asp	ggt Gly	gtc Val	att Ile	gtg Val 815	gtc Val	2448
45	atc Ile	agc Ser	gtg Val	tgg Trp 820	gag Glu	atc Ile	gtg Val	ggc Gly	cag Gln 825	cag Gln	Gly ggg	ggc Gly	ggc Gly	ctg Leu 830	tcg Ser	gtg Val	2496
50	ctg Leu	cgg Arg	acc Thr 835	ttc Phe	cgc Arg	ctg Leu	atg Met	cgt Arg 840	gtg Val	ctg Leu	aag Lys	ctg Leu	gtg Val 845	cgc Arg	ttc Phe	ctg Leu	2544
	ccg Pro	gcg Ala 850	ctg Leu	cag Gln	cgg Arg	cag Gln	ctg Leu 855	gtg Val	gtg Val	ctc Leu	atg Met	aag Lys 860	acc Thr	atg Met	gac Asp	aac Asn	2592
<i>55</i>	gtg Val 865	gcc Ala	acc Thr	ttc Phe	tgc Cys	atg Met 870	ctg Leu	ctt Leu	atg Met	ctc Leu	ttc Phe 875	atc Ile	ttc Phe	atc Ile	ttc Phe	agc Ser 880	2640
60	atc Ile	ctg Leu	ggc Gly	atg Met	cat His 885	ctc Leu	ttc Phe	ggc Gly	tgc Cys	aag Lys 890	ttt Phe	gcc Ala	tct Ser	gag Glu	cgg Arg 895	gat Asp	2688
	ggg Gly	gac Asp	acc Thr	ctg Leu	cca Pro	gac Asp	cgg Arg	aag Lys	aat Asn	ttt Phe	gac Asp	tcc Ser	ttg Leu	ctc Leu	tgg Trp	gcc Ala	2736

				900					905					910			
5	atc Ile	gtc Val	act Thr 915	gtc Val	ttt Phe	cag Gln	atc Ile	ctg Leu 920	Thr	cag Gln	gag Glu	gac Asp	tgg Trp 925	aac Asn	aaa Lys	gtc Val	2784
10	ctc Leu	tac Tyr 930	aat Asn	ggt Gly	atg Met	gcc Ala	tcc Ser 935	acg Thr	tcg Ser	tcc Ser	tgg Trp	gcg Ala 940	gcc Ala	ctt Leu	tat Tyr	ttc Phe	2832
10	att Ile 945	gcc Ala	ctc Leu	atg Met	acc Thr	ttc Phe 950	ggc Gly	aac Asn	tac Tyr	gtg Val	ctc Leu 955	ttc Phe	aat Asn	ttg Leu	ctg Leu	gtc Val 960	2880
15	gcc Ala	att Ile	ctg Leu	gtg Val	gag Glu 965	ggc Gly	ttc Phe	cag Gln	gcg Ala	gag Glu 970	gga Gly	gat Asp	gcc Ala	aac Asn	aag Lys 975	tcc Ser	2928
20	gaa Glu	tca Ser	gag Glu	ccc Pro 980	gat Asp	ttc Phe	ttc Phe	tca Ser	ccc Pro 985	agc Ser	ctg Leu	gat Asp	ggt Gly	gat Asp 990	Glγ. ggg	gac Asp	2976
25	agg Arg	aag Lys	aag Lys 995	tgc Cys	ttg Leu	gcc Ala	Leu	gtg Val LOOO	tcc Ser	ctg Leu	gga Gly	Glu	cac His 1005	ccg Pro	gag Glu	ctg Leu	3024
30	Arg	aag Lys 1010	agc Ser	ctg Leu	ctg Leu	Pro	cct Pro 1015	ctc Leu	atc Ile	atc Ile	His	acg Thr 1020	gcc Ala	gcc Ala	aca Thr	ccc Pro	3072
	atg Met 1025	Ser	ctg Leu	ccc ⁻ Pro	Lys	agc Ser 1030	acc Thr	agc Ser	acg Thr	Gly	ctg Leu 1035	ggc Gly	gag Glu	gcg Ala	Leu	ggc Gly 1040	3120
35	cct Pro	gcg Ala	tcg Ser	Arg	cgc Arg 1045	Thr	agc Ser	agc Ser	agc Ser	ggg Gly 1050	tcg Ser	gca Ala	gag Glu	Pro	ggg Gly 1055	gcg Ala	3168
40	gcc Ala	cac His	Glu	atg Met .060	aag Lys	tca Ser	ccg Pro	Pro	agc Ser 1065	gcc Ala	cgc Arg	agc Ser	Ser	ccg Pro 1070	cac His	agc Ser	3216
45	Pro	Trp	agc Ser .075	Ala	gca Ala	Ser	agc Ser 1	Trp	acc Thr	agc Ser	agg Arg	Arg	tcc Ser .085	agc Ser	cgg Arg	aac Asn	3264
50	Ser	ctc Leu 090	ggc Gly	cgt Arg	gca Ala	Pro-	agc Ser 095	ctg Leu	aag Lys	cgg Arg	Arg	agc Ser 100	cca Pro	agt Ser	gga Gly	gag Glu	3312
	cgg Arg 1105	Arg	tcc Ser	ctg Leu	Leu	tcg Ser 110	gga Gly	gaa Glu	ggc Gly	Gln	gag Glu 115	agc Ser	cag Gln	gat Asp	Glu	gag Glu 120	3360
<i>55</i>	gag Glu	agc Ser	tca Ser	Glu	gag Glu 125	gag Glu	cgg Arg	gcc Ala		cct Pro 130	gcg Ala	ggc Gly	agt Ser	Asp	cat His	cgc Arg	3408
60	cac His	agg Arg	Gly	tcc Ser 140	ctg Leu	gag Glu	cgg Arg	Glu	gcc Ala 145	aag Lys	agt Ser	tcc Ser	Phe	gac Asp 150	ctg Leu	cca Pro	3456
	gac Asp	aca Thr	ctg Leu	cag Gln	gtg Val	cca Pro	ggg Gly	ctg Leu	cat His	cgc Arg	act Thr	gcc Ala	agt Ser	ggc Gly	cga Arg	Gly	3504

	1155		1160	1165	
5	tot got tot Ser Ala Ser 1170	Glu His Gln	gac tgc aat Asp Cys Asn 175	ggc aag tcg gct tca Gly Lys Ser Ala Ser 1180	ggg cgc 3552 Gly Arg
10	ctg gcc cgg Leu Ala Arg 1185	gcc ctg cgg Ala Leu Arg 1190	cct gat gac Pro Asp Asp	ccc cca ctg gat ggc Pro Pro Leu Asp Gly 1195	gat gac 3600 Asp Asp 1200
	gcc gat gac Ala Asp Asp	gag ggc aac Glu Gly Asn 1205	Leu Ser Lys	ggg gaa cgg gtc cgc Gly Glu Arg Val Arg .210	gcg tgg 3648 Ala Trp 1215
15	Ile Arg Ala	cga ctc cct Arg Leu Pro 1220	gcc tgc tgc Ala Cys Cys 1225	ctc gag cga gac tcc Leu Glu Arg Asp Ser 1230	Trp Ser
20	gcc tac atc Ala Tyr Ile 1235	ttc cct cct Phe Pro Pro	cag tcc agg Gln Ser Arg 1240	ttc cgc ctc ctg tgt Phe Arg Leu Leu Cys 1245	cac cgg 3744 His Arg
25	atc atc acc Ile Ile Thr 1250	His Lys Met	ttc gac cac Phe Asp His 255	gtg gtc ctt gtc atc Val Val Leu Val Ile 1260	atc ttc 3792 Ile Phe
30	ctt aac tgc Leu Asn Cys 1265	atc acc atc Ile Thr Ile 1270	gcc atg gag Ala Met Glu	cgc ccc aaa att gac Arg Pro Lys Ile Asp 1275	ccc cac 3840 Pro His 1280
	agc gct gaa Ser Ala Glu	egc atc ttc Arg Ile Phe 1285	Leu Thr Leu	tcc aat tac atc ttc Ser Asn Tyr Ile Phe 290	acc gca 3888 Thr Ala 1295
35	Val Phe Leu	gct gaa atg Ala Glu Met. 1300	aca gtg aag Thr Val Lys 1305	gtg gtg gca ctg ggc Val Val Ala Leu Gly 1310	Trp:Cys
40	ttc ggg gag Phe Gly Glu. 1315	cag gcg tac Gln Ala Tyr	ctg cgg agc Leu Arg Ser 1320	agt tgg aac gtg ctg Ser Trp Asn Val Leu 1325	gac ggg 3984 Asp Gly
45	ctg ttg gtg Leu Leu Val 1330	ctc atc tcc Leu Ile Ser 1	Val Ile Asp	att ctg gtg tcc atg Ile Leu Val Ser Met 1340	gtc tct 4032 Val Ser
50	gac agc ggc Asp Ser Gly 1345	acc aag atc Thr Lys Ile 1350	ctg ggc atg Leu Gly Met	ctg agg gtg ctg.cgg Leu Arg Val Leu Arg 1355	ctg ctg 4080 Leu Leu 1360
	cgg acc ctg .Arg Thr Leu	cgc ccg ctc Arg Pro Leu 1365	Arg Val Ile	agc cgg gcg cag ggg Ser Arg Ala Gln Gly 370	ctg aag 4128 Leu Lys 1375
<i>55</i> .	Leu Val Val	gag acg ctg Glu Thr Leu 1380	atg tcc tca Met Ser Ser 1385	ctg aaa ccc atc ggc Leu Lys Pro Ile Gly 1390	Asn Ile
60	gta gtc atc Val Val Ile 1395	tgc tgt gcc Cys Cys Ala	ttc ttc atc Phe Phe Ile 1400	att ttc ggc atc ttg Ile Phe Gly Ile Leu 1405	ggg.gtg 4224 Gly Val
	cag ctc ttc Gln Leu Phe	aaa ggg aag Lys Gly Lys	ttt ttc gtg. Phe Phe Val	tgc cag ggc gag gat Cys Gln Gly, Glu Asp	acc agg 4272 Thr Arg

	1410				1415					1420					
5	aac atc Asn Ile 1425	acc a Thr A	s n Lys	tcg Ser 1430	gac Asp	tgt Cys	gcc Ala	Glu	gcc Ala 1435	agt Ser	tac Tyr	cgg Arg	Trp	gtc Val 1440	4320
10	cgg cac Arg His	aag t Lys T	ac aac yr Asn 1445	ttt Phe	gac Asp	aac Asn	Leu	ggc Gly 1450	cag Gln	gcc Ala	ctg Leu	Met	tcc Ser 1455	ctg Leu	4368
	ttc gtt Phe Val	ttg g Leu A 14	la Ser	aag Lys	gat Asp	Gly	tgg Trp 1465	gtg Val	gac Asp	atc Ile	Met	tac Tyr 1470	gat Asp	ggg Gly	4416
15	ctg gat Leu Asp	gct g Ala V 1475	tg ggc al Gly	gtg Val	Asp	cag Gln 1480	cag Gln	ccc Pro	atc Ile	Met	aac Asn 1485	cac His	aac Asn	ccc Pro	4464
20	tgg atg Trp Met 1490	ctg c Leu L	tg tac eu Tyr	Phe	atc Ile 1495	tcg Ser	ttc Phe	ctg Leu	Leu	att Ile 1500	gtg Val	gcc Ala	ttc Phe	ttt Phe	4512
25	gtc ctg Val Leu 1505	aac a Asn M	et Phe	gtg Val 1510	ggt Gly	gtg Val	gtg Val	Val	gag Glu 1515	aac Asn	ttc Phe	cac His	Lys	tgt Cys 1520	4560
30	cgg cag Arg Gln	cac c His G	ag gag ln Glu 1525	gaa Glu	gag Glu	gag Glu	Ala	cgg Arg 1530	cgg Arg	cgg Arg	gag Glu	Glu	aag Lys 1535	cgc Arg	4608
	cta cga Leu Arg	aga c Arg L	eu Glu	aaa Lys	aag Lys	Arg	agg Arg 1545	aat Asn	cta Leu	atg Met	Leu	gac Asp 1550	gat Asp	gta Val	465 <u>6</u>
35	att gct Ile Ala	tcc go Ser G 1555	gc agc ly Ser	tca Ser	Ala	agc Ser 1560	gct Ala	gcg Ala	tca Ser	Glu	gcc Ala 1565	cag Gln	tgc Cys	aaa Lys	4704
40	cct tac Pro Tyr 1570	tac to Tyr So	cc gac er Asp	Tyr	tcc Ser 575	cgc Arg	ttc Phe	cgg Arg	Leu	ctc Leu .580	gtc Val	cac His	cac His	ttg Leu	4752
45	tgc acc Cys Thr 1585	agc ca Ser H	is Tyr	ctg Leu 1590	gac Asp	ctc Leu	ttc Phe	Ile	aca Thr 595	ggt Gly	gtc Val	atc Ile	Gly	ctg Leu .600	4800
50	aac gtg Asn Val	gtc ac Val Ti	cc atg nr Met 1605	gcc Ala	atg Met	gag Glu	His	tac Tyr 1610	cag Gln	cag Gln	ccc Pro	Gln	att Ile 1615	ctg Leu	4848
	gat gag Asp Glu	gct ct Ala Le 162	eu Lys	atc Ile	tgc Cys	Asn	tac Tyr 1625	atc Ile	ttc Phe	act Thr	Val	atc Ile 1630	ttt Phe	gtc Val	4896
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	atg ggc Met Gly	atc ac Ile Ti	eg ctg nr Leu	gag .Glu	gaa Glu	atc Ile	gag Glu	gtc Val	aac Asn	gcc Ala	tcg Ser	ctg Leu	ccc Pro	atc Ile	5040

	1665		1670		1675		1680
5	aac ccc Asn Pro	Thr Ile	atc cgc at Ile Arg Il 685	c atg agg e Met Arc	g gtg ctg c g Val Leu A 1690	ege att gee eg Arg Ile Ala Ar 169	g Val
10	ctg aag Leu Lys	ctg ctg Leu Leu 1700	aag atg gc Lys Met Al	t gtg ggd a Val Gly 1705	/ Met Arg A	gcg ctg ctg ga Ala Leu Leu As 1710	c acg 5136 p Thr
•	Val Met	cag gcc Gln Ala : 1715	ctg ccc ca Leu Pro Gl	g gtg ggç n Val Gly 1720	g aac ctg g v Asn Leu G	gga ctt ctc tt Gly Leu Leu Ph 1725	c atg 5184 e Met
15	ttg ttg Leu Leu 1730	ttt ttc a	atc ttt gc Ile Phe Al 173	a Ala Leu	ı Gly Val G	gag ctc ttt gg: Glu Leu Phe Gl: 740	a gac 5232 y Asp.
20	ctg gag Leu Glu 1745	tgt gac (Cys Asp (gag aca ca Glu Thr Hi 1750	c ccc tgt s Pro Cys	gag ggc c Glu Gly L 1755	etg ggc cgt ca Leu Gly Arg His	t gcc 5280 s Ala 1760
25	acc ttt Thr Phe	Arg Asn I	ttt ggc ato Phe Gly Met 765	g gcc ttc t Ala Phe	cta acc c Leu Thr L 1770	etc ttc cga gto Leu Phe Arg Val 1779	l Ser
30	aca ggt Thr Gly	gac aat t Asp Asn 1 1780	igg aat ggo Irp Asn Gly	c att atg y Ile Met 1785	Lys Asp T	cc ctc cgg gad hr Leu Arg Asp 1790	tgt 5376 Cys
	Asp Gin	gag tcc a Glu Ser 1 795	acc tgc tac Thr Cys Tyi	aac acg Asn Thr 1800	gtc atc t Val Ile S	cg cct atc tac er Pro Ile Tyr 1805	c ttt .5424 Phe
35	gtg tcc Val Ser 1810	ttc gtg c Phe Val I	etg acg gcd Leu Thr Ala 1815	a Gln Phe	gtg cta g Val Leu V 183	tc aac gtg gtg al Asn Val Val 20	g atc 5472 . Ile
40	gcc gtg Ala Val 1825	ctg atg a Leu Met I	ag cac cto Lys His Leo 1830	g gag gag ı Glu Glu	agc aac aa Ser Asn Ly 1835	ag gag gcc aag ys Glu Ala Lys	g gag
45	gag gcc Glu Ala	Glu Leu G	Slu Ala Glu	g ctg gag 1 Leu Glu	Leu Glu Me	tg aag acc ctc et Lys Thr Leu .1855	Ser
50	ccc cag Pro Gln	ccc cac t Pro His S 1860	cg cca ctg er Pro Leu	ggc agc Gly Ser 1865	ccc ttc ct Pro Phe Le	tc tgg cct ggg eu Trp Pro Gly 1870	gtc 5616 Val
50	Glu Gly	ccc gac a Pro Asp S 875	gc ccc gac er Pro Asp	agc ccc Ser Pro 1880	aag cct go Lys Pro Gl	gg gct ctg cac ly Ala Leu His 1885	cca 5664 Pro
<i>55</i>	gcg gcc (Ala Ala (1890	cac gcg a His Ala A	ga tca gcc rg Ser Ala 1895	Ser His	ttt tcc ct Phe Ser Le	tg gag cac ccc eu Glu His Pro 00	acg 5712 Thr
60	atg cag o Met Gln 1 1905	ccc cac c Pro His P	cc acg gag ro Thr Glu 1910	ctg cca Leu Pro.	gga cca ga Gly Pro As 1915	ac tta ctg act sp Leu Leu Thr	gtg 5760 Val 1920
	cgg aag 1 Arg Lys :	tct ggg g Ser Gly V	tc agc cga al Ser Arg	acg cac Thr His	tct ctg cc Ser Leu Pr	cc aat gac agc ro Asn Asp Ser	tac 5808 Tyr

	19	25	1930	1935	
5	atg tgt cgg cat g Met Cys Arg His G 1940	gg agc act gc ly Ser Thr Al	c gag ggg ccc c a Glu Gly Pro La 1945	tg gga cac agg ggc eu Gly His Arg Gly 1950	5856
10	tgg ggg ctc ccc a Trp Gly Leu Pro L 1955	aa got cag to ys Ala Gln Se 196	r Gly Ser Val Le	tg too gtt cac too eu Ser Val His Ser 1965	5904
	cag cca gca gat a Gln Pro Ala Asp T 1970	oc ago tac ato or Ser Tyr Ile 1975	c ctg cag ctt co e Leu Gln Leu Pi 198	cc aaa gat gca cct ro Lys Asp Ala Pro 30	5952
15	cat ctg ctc cag con His Leu Leu Gln P. 1985	cc cac age geo ro His Ser Ala 1990	c cca acc tgg gc a Pro Thr Trp Gl 1995	gc acc atc ccc aaa ly Thr Ile Pro Lys 2000	6000
20	ctg ccc cca cca go Leu Pro Pro Pro G 200	ly Arg Ser Pro	t ttg gct cag ac o Leu Ala Gln Ar 2010	gg cca ctc agg cgc cg Pro Leu Arg Arg 2015	6048
25	cag gca gca ata aq Gln Ala Ala Ile An 2020	gg act gac too gg Thr Asp Sei	e ttg gac gtt ca r Leu Asp Val Gl 2025	ag ggt ctg ggc agc in Gly Leu Gly Ser 2030	6096
30	cgg gaa gac ctg ct Arg Glu Asp Leu Le 2035	g gca gag gto eu Ala Glu Val 2040	l Ser Gly Pro Se	cc ccg ccc ctg gcc er Pro Pro Leu Ala 2045	6144
	cgg gcc tac tct tt Arg Ala Tyr Ser Pr 2050	c tgg ggc cac ne Trp Gly Glr 2055	g tca agt acc ca n Ser Ser Thr Gl 206	g gca cag cag cac n Ala Gln Gln His 50	6192
35	tcc cgc agc cac ag Ser Arg Ser His Se 2065	gc aag atc tco er Lys Ile Ser 2070	c aag cac atg ac c Lys His Met Th 2075	cc ccg cca gcc cct or Pro Pro Ala Pro 2080	6240
40	tgc cca ggc cca ga Cys Pro Gly Pro Gl 208	u Pro Asn Trp	g ggc aag ggc cc o Gly Lys Gly Pr 2090	t cca gag acc aga o Pro Glu Thr Arg 2095	6288
45	agc agc tta gag tt Ser Ser Leu Glu Le 2100	g gac acg gag u Asp Thr Glu	g ctg agc tgg at 1 Leu Ser Trp Il 2105	t tca gga gac ctc e Ser Gly Asp Leu 2110	6336
50	ctg ccc cct ggc gg Leu Pro Pro Gly Gl 2115	c cag gag gag y Gln Glu Glu 21:20	ı Pro Pro Ser Pr	a cgg gac ctg aag o Arg Asp Leu Lys 2125	6384
	aag tgc tac agc gt Lys Cys Tyr Ser Va 2130	g gag gcc cag l Glu Ala Gln 2135	g agc tgc cag cg n Ser Cys Gln Ar 214		6432
<i>55</i>	tgg ctg gat gag ca Trp Leu Asp Glu Gl 2145	g agg aga cac n Arg Arg His 2150	tct atc gcc gt Ser Ile Ala Va 2155	c agc tgc ctg gac l Ser Cys Leu Asp 2160	6480
60	agc ggc tcc caa cc Ser Gly Ser Gln Pr 216	o His Leu Gly	aca gac ccc tc Thr Asp Pro Se 2170	t aac ctt ggg ggc r Asn Leu Gly Gly 2175	6528
	cag cct ctt ggg gg Gln Pro Leu Gly Gl	g cct ggg agc y Pro Gly Ser	cgg ccc aag aa Arg Pro Lys Ly	a aaa ctc agc ccg s Lys Leu Ser Pro	6576

	2180	2135	2190	
3	cot agt ato acc ata ga Pro Ser Ile Thr Ile As 2195	p Pro Pro Glu S 2200 .	ago caa ggt cot ogg ac Ser Gln Gly Pro Arg Th 2205	c ccg 6624 r Pro
10	coc ago cot ggt ato to Pro Ser Pro Gly Ile Cy 2210	c ctc cgg agg a s Leu Arg Arg A 2215	egg gót cog too ago ga erg Ala Pro Ser Ser As 2220	c tcs 6672 p Ser
10	aag gat ooc ttg goo to Lys Asp Pro Leu Ala Se 2225 223	r Gly Pro Pro A	ac ago atg got goc to sp Ser Met Ala Ala Se 2235	g ccc 6720 r Pro 2240
15	toc cca aag aaa gat gt Ser Pro Lys Lys Asp Va 2245	l Leu Ser Leu S	cc ggt tta tcc tot gas er Gly Leu Ser Ser As 50 225	o Pro
20	gca gac ctg gac ccc Ala Asp Leu Asp Pro 2260			6783
25	<210> 3 <211> 6804 <212> DNA <213> Homo sapiens			·
30	<220> <221> CDS <222> (1)(6804)			
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40	cgg agc ttc atg cgg ct Arg Ser Phe Met Arg Le 20	c aac gac ctg t u Asn Asp Leu S 25	cg ggg gcc ggg ggg cgg er Gly Ala Gly Gly Arg 30	g ccg 96 g Pro
45	ggg ccg ggg tca gca ga Gly Pro Gly Ser Ala Gl 35	a aag gac ccg g 1 Lys Asp Pro G 40	ge age geg gae tee gag ly Ser Ala Asp Ser Glu 45	ggg 144 Ala
	gag ggg ctg ccg tac cc Glu Gly Leu Pro Tyr Pro 50			
50	agc cag gac agc cgc cc Ser Gln Asp Ser Arg Pro 65	Arg Ser Trp C	gt ctc cgc acg gtc tgt ys Leu Arg Thr Val Cys 75	aac 240 Asn 80
<i>55</i>	ccc tgg ttt gag cgc atc Pro Trp Phe Glu Arg Il: 85	e Ser Met Leu Va	to ato ott oto aac tgo al Tle Leu Leu Asn Cys 90 95	Val
60	acc ctg ggc atg ttc cgc Thr Leu Gly Met Phe Arc 100.	g cca tgc gag ga g Pro Cys Glu As 105	ac atc gcc tgt gac tcc sp Ile Ala Cys Asp Ser 110	cag 336 Gln
	cgc tgc cgg atc ctg cac Arg Cys Arg Ile Leu Gl: 115	g god tit gat ga n Ala Phe Asp As n 120	ac tto ato ttt god tto sp Phe Ile Phe Ala Phe 125	ttt 384 Phe

5	gcc Ala	gtg Val 130	gag Glu	atg Met	gtg Val	gtg Val	aag Lys 135	atg Met	gtg Val	gcc Ala	ttg Leu	ggc Gly 140	atc Ile	ttt Phe	Gly 333	aaa Lys	432
	aag Lys 145	tgt Cys	tac Tyr	ctg Leu	gga Gly	gac Asp 150	act Thr	Lib	aac Asn	cgg Arg	ctt Leu 155	gac Asp	titt Phe	tta Phe	atc Ile	gtc Val 160	480
10	atc Ile	gca Ala	ggg Gly	a'tg Met	ctg Leu 165	gag Glu	tac Tyr	tog Ser	ctg Leu	gac Asp 170	ctg Leu	cag Gln	aac Asn	gtc Val	agc Ser 175	ttc Phe	528
15	tca Ser	gct Ala	gtc Val	agg Arg 180	aca Thr	gtc Val	cgt Arg	gtg Val	ctg Leu 185	cga Arg	ccg Pro	ctc Leu	agg Arg	gcc Ala 190	att īle	aac Asn	576.
20															acg Thr		624
25	ccc Pro	atg Met 210	ctg Leu	ggc Gly	aac Asn	gtc Val	ctg Leu 215	ctg Leu	ctc Leu	tğc Cys	ttc Phe	ttc Phe 220	gtc Val	ttc Phe	ttc Phe	atc Ile	672
															aac Asn		720
30															ctg Leu 255		768
35															tgc Cys		816
40															acg Thr		864
<i>45</i>															gag Glu		912
															tac Tyr		960
50															atc Ile 335		1008
<i>55</i>	ttt Phe	gac Asp	aac Asn	att Ile 340	ggc Gly	tat Tyr	gcc Ala	tgg Trp	atc Ile 345	gcc Ala	atc īle	ttc Phe	cag Gln	gtc Val 350	atc Ile	acg Thr	1056
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	ttc Phe	tac Tyr 370	aat Asn	ttc Phe	atc Ile	tac Tyr	ttc Phe 375	atc Ile	ctc Leu	ctc Leu	atc Ile	atc Ile 380	gtg Val	ggc Gly	tcc Ser	ttc Phe	1152

<i>5</i>	ttc Phe 385	atg Met	atc Ile	aac Asn	ctg Leu	tgc Cys 390	ctg Leu	gig Val	gtg Val	att	gcc Ala 395	acg Thr	cag Gln	tto Phe	tca Ser	gag Glu 400	1200
J	acc Thr	aag Lys	cag Gln	cgg Arg	gaa Glu 405	agc Ser	cag Gln	otg Leju	atg Met	cgg Arg 410	gag Glu	cag Gln	ogt Arg	gig Val	ogg Arg 415	ttc Phe	1248
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20	cgc Arg	agg Arg 450	ctg Leu	gct Ala	cag Gln	gtc Val	tct Ser 455	cgg Arg	gca Ala	gca Ala	ggt Gly	gtg Val 460	cgg Arg	gtt Val	ggg Gly	ctg Leu	1392
25	ctc Leu 465	agc Ser	agc Ser	cca Pro	gca Ala	ccc Pro 470	ctc Leu	Gl À aaa	gjy ggc	cag Gln	gag Glu 475	acc Thr	cag Gln	ccc Pro	agc Ser	agc Ser 480	1440
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30	cac His	cac His	cac His	cac His 500	cat His	cac His	cac His	cac His	tac Tyr 505	cac His	ctg Leu	ggc Gly	aat Asn	ggg Gly 510	acg Thr	ctc Leu	1536
35	agg Arg	gcc Ala	ccc Pro 515	cgg Arg	gcc Ala	agc Ser	ccg Pro	gag Glu 520	atc Ile	cag Gln	gac Asp	agg Arg	gat Asp 525	gcc Ala	aat Asn	Gly	1584
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60	gag Glu	gtg Val 610	Ala	gcc Ala	agc Ser	tct Ser	gag Gly 615	Pro	cca Pro	acc Thr	ctc Leu	acc Thr 620	agc Se∵	ctc Leu	aac Asn	atc Ile	1372
	cca Pro 625	Pro	Gly	ccc	tac Tyr	agc Ser 630	Ser	atg Met	cac His	aag Lys	ctg Leu 635	Leu	gag Glu	aca Thr	cag Gln	agt Ser 640	1920

5	aca Thr	ggt Gly	gcc Ala	tgc Cys	caa Gln 645	agc Ser	to: Ser	tgc Cys	aag Lys	atc Ile 650	Ser	ago Ser	Pro	tgo Cys	ttg Leu 655	aaa Lys	1963
	gca Ala	gac Asp	agt Ser	gga Gly 660	gee Ala	tgt Cys	ggt Gly	cca Pro	gac Asp 665	agc Ser	tgc Cys	ccc Pro	tac .Tyr	tgt Cys 670	goo Ala	ogg Arg	2016
1:0	gcc Ala	G] À ààà	gca Ala 675	Gl À āāā	gag Glu	gtg Val	gag Glu	ctc Leu 680	gcc Ala	gac Asp	ogt Arg	gaa Glu	atg Met 685	cct Pro	gac Asp	tca Ser	2064
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25	gag Glu	ccc Pro	agc Ser	tcț Ser	gtg Val 725	Leu	gcc Ala	ttc Phe	tgg Trp	agg Arg 730	cta Leu	atc Ile	tgt. Cys	gac Asp	acc Thr 735	ttc Phe	2208
	cga Arg	aag Lys	att Ile	gtg Val 740	gac Asp	agc Ser	aag Lys	tac Tyr	ttt Phe 745	ggc Gly	cgg Arg	gga Gly	atc Ile	atg Met 750	atc Ile	gcc Ala	. 2256
30	atc Ile	ctg Leu	gtc Val 755	aac Asn	aca Thr	ctc Leu	agc Ser	atg Met 760	ggc Gly	atc Ile	gaa Glu	tac Tyr	cac His 765	gag Glu	cag Gln	ccc Pro	2304
35	gag Glu	gag Glu 770	ctt Leu	acc Thr	aac Asn	gcc Ala	cta Leu 775	gaa Glu	atc Ile	agc Ser	aac Asn	atc Ile 780	gtc Val	ttc Phe	acc Thr	agc Ser	2352
40	ctc Leu 785	ttt Phe	gcc Ala	ctg Leu	gag Glu	atg Met 790	ctg Leu	ctg Leu	aag Lys	ctg Leu	ctt Leu 795	gtg Val	tat Tyr	ggt Gly	ccc. Pro.	ttt Phe 800	2400
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	atc Ile	agc Ser	gtg Val	tgg Trp 820	gag Glu	atc Ile	gtg Val	ggc Gly	cag Gln 825	cag Gln	G] À āāā	ggc Gly	ggc Gly	ctg Leu 830	tcg Ser	gtg Val	2496
50	ctg Leu	cgg Arg	acc Thr 835	ttc Phe	cgc Arg	ctg Leu	atg Met	cgt Arg 840	gtg Val	ctg Leu	aag Lys	ctg Leu	gtg Val 845	cgc Arg	ttc Phe	ctg Leu	2544
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60	gtg Val 865	gcc Ala	acc Thr	ttc Phe	tgc Cys	atg Met 870	ctg Leu	ctt Leu	atg Met	ctc Leu	ttc Phe 875	atc Ile	ttc Phe	atc Ile	Phe	agc Ser 380	2640
	atc Ile	ctg Leu	ggc Gly	atg Met	cat His 885	ctc Leu	ttc Phe	ggc Gly	tgc Cys	aag L <u>v</u> s 890	ttt Phe	gcc Ala	tct Ser	gag Glu	892 Yra caa	gat Asp	2688

<i>5</i>	Gly	gac Asp	acc Thr	ctg Leu 900	cca Pro	ysb dec	Arg	aag Lys	aat Asn 905	ttt Phe	gac Asp	tcc Ser	ttg Leu	ctc Leu 910	tgg Trp	gcc Ala	2736
-	atc Ile	gtc Val	act Thr 915	gtc Val	ttt Phe	cag Gln	atc Ile	ctg Leu 920	acc Thr	cag Gln	gag Glu	gac Asp	tgg Trp 925	aac Asn	aaa Lys	gts Val	2784
10	ctc Leu	tac Tyr 930	aat Asn	ggt Gly	atg Met	gcc Ala	Ser 935	acg Thr	tcg Ser	tcc Ser	tgg Trp	gcg Ala 940	gcc Ala	ctt Leu	tat Tyr	ttc Phe	2832
15	att Ile 945	gcc Ala	ctc Leu	atg Met	acc Thr	ttc Phe 950	GļĀ	aac Asn	tac Tyr	gtg Val	ctc Leu 955	ttc Phe	aat Asn	ttg Leu	ctg Leu	gtc Val 960	2830
20	gcc Ala	att Ile	ctg Leu	gtg Val	gag Glu 965	ggs Gly	ttc Phe	cag Gln	gcg Ala	gag Glu 970	gga Gly	gat Asp	gcc Ala	aac Asn	aag Lys 975	tcc Ser	2928
25	gaa Glu	tca Ser	gag Glu	ccc Pro 980	gat Asp	ttc Phe	ttc Phe	tca Ser	ccc Pro 985	agc Ser	ctg Leu	gat Asp	ggt Gly	gat Asp 990	GļĀ āāā	gac Asp	2976
	agg Arg	aag Lys	aag Lys 995	tgc Cys	ttg Leu	gcc Ala	Leu	gtg Val 1000	tcc Ser	ctg Leu	gga Gly	Glu	cac His 1005	ccg Pro	gag Glu	ctg Leu	3024
30	Arg	aag Lys L010	agc Ser	ctg Leu	ctg Leu	₽ro	cct Pro 015	ctc Leu	atc Ile	atc Ile	His	acg Thr 020	gcc Ala	gcc Ala	aca Thr	ccc Pro	3072
35	atg Met 1025	Ser	ctg Leu	ccc Pro	Lys	agc Ser 1030	acc Thr	agc Ser	acg Thr	Gly	ctg Leu 1035	ggc Gly	gag Glu	gcg Ala	ctg Leu]	ggc Gly .040	3120
40	cct Pro	gcg Ala	tcg Ser	Arg	cgc. Arg 1045	acc Thr	agc Ser	agc Ser	Ser	ggg Gly .050	tcg Ser	gca Ala	gag Glu	Pro	ggg Gly. 1055	gcg Ala	3168
4 5	gcc Ala	cac His	Glu	atg Met 1060	aag Lys	tca Ser	ccg Pro	Pro	agc Ser .065	gcc Ala	cgc Arg	agc Ser	Ser	ccg Pro .070	cac His	agc Ser	3216
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<i>55</i>		Arg			Leu					Gln					gaa Glu 1		3360
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	cac His	agg Arg	Gly	tcc Ser .140	ctş Leu	gag. Glu	cgg Arg	Glu ·	gcc Ala 145	aag Lys	agt Ser	tcc Ser	Phe	gac Asp 150	ctg Leu	cca Pro	3456

<u>5</u>		Thr					Gly					Ala	agt Ser 1165				3504
	Ser					Gln					Lys		gct Ala				3552
10		Ala			Leu					Pro			gat Asp		Asp		3600
15				Glu					Lys				gtc Val	Arg			3648
20			Ala					Cys					gac Asp				3696
25	gcc Ala	Tyr	atc Ile 1235	ttc Phe	cct Pro	cct Pro	Gln	tcc Ser .240	agg Arg	ttc Phe	cgc Arg	Leu	ctg Leu L245	tgt Cys	cac His	cgg Arg	3744
	Ile					Met					Val		gtc Val				3792
30		Asn			Thr					Arg			att Ile		Pro		3840
35				Arg					Leu				atc Ile	Phe			3888.
40			Leu					Val					ctg Leu 1				3936
45		Gly					Leu					Asn	gtg Val L325				3984
	Leu					Ser					Leu		tcc Ser				4032
50	gac Asp 1345	Ser	ggc Gly	acc Thr	Lys	atc Ile 1350	ctg Leu	ggc Gly	atg Met	Leu	agg Arg 1355	gtg Val	ctg Leu	cgg Arg	Leu	ctg Leu 1360	4080
<i>55</i>	cgg Arg	acc Thr	ctg Leu	Arg	ccg Pro 1365	ctc Leu	agg Arg	gtg Val	Ile	agc Ser 1370	cgg Arg	gcg Ala	cag Gln	Gly	ctg Leu 1375	aag Lys	4128
60			Val					Ser					atc Ile				4176
		Val					Phe					Gly	atc Ile 1405				4224

5	cag cto Gln Leu 1410	Phe	aaa Lys	G1 y	Lys	ttt Phe 1415	tt: Phe	gtg Val	tgo Cys	Gln	ggc Gly 1420	Glu	gat Asp	acc The	agg. Arg	÷272
	aac atc Asn Ile 1425	acc Thr	aat Asn	Lys	tcg Ser 1430	Asp	tgt Cys	gcc Ala	Glu	gcc Ala 1435	Ser	tac Tyr	Arg cgg	tgg Trp	gtc Val 1440	∔320
10	cgg cac Arg His	aag Lys	Tyr	aac Asn 1445	ttt Phe	gac Asp	aac Asn	Leu	ggc Gly 1450	cag Gln	gcc Ala	ctg Leu	Met	tcc Ser 1455	Leu	÷363
15	tto git Phe Val	Leu	gcc Ala 1460	tcc Ser	aag Lys	gat Asp	Gly	tgg Trp 1465	gtg -Val	gac Asp	atc Ile	Met	tac Tyr 1470	gat Asp	Gly	4416
20	ctg gat Leu Asp	gct Ala 1475	gtg Val	ggc Gly	gtg Val	Asp	cag Gln 1480	cag Gln	ccc Pro	atc Ile	Met	aac Asn 1485	cac His	aac Asn	ccc Pro	4464
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	gtc ctg Val Leu 1505	aac Asn	atg Met	Phe	gtg Val L510	ggt Gly	gtg Val	gtg Val	Val	gag Glu L515	aac Asn	ttc Phe	cac His	Lys	tgt Cys 1520	4560
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35	cta cga Leu Arg	Arg	ctg Leu .540	gag Glu	aaa Lys	aag Lys	Arg	agg Arg L545	agt Ser	aag Lys	gag Glu	Lys	cag Gln .550	atg Met	gct Ala	4656
40	gat cta Asp Leu	atg Met .555	ctg Leu	gac Asp	gat Asp	Val	att Ile 560	gct Ala	tcc Ser	ggc Gly	Ser	tca Ser 565	gcc Ala	agc Ser	gct Ala	4704
45	gcg tca Ala Ser 1570	gaa Glu	gcc Ala	cag Gln	Cys	aaa Lys 575	cct Pro	tac Tyr	tac Tyr	Ser	gac Asp 580	tac Tyr	tcc Ser	cgc Arg	ttc Phe	4 752
	cgg ctc Arg Leu 1585	ctc Leu	gtc Val	His	cac His 590	ttg Leu	tgc Cys	acc Thr	Ser	cac His 595	tac Tyr	ctg Leu	gac Asp	Leu	ttc Phe 1600	4900
50	atc aca Ile Thr	ggt Gly	Val	atc Ile 605	Gly ggg	ctg Leu	aac Asn	Val	gtc Val 610	acc Thr	atg Met	gcc Ala	Met	gag Glu 615	cac His	4848
<i>55</i>	tac cag Tyr Gln	Gln	ccc Pro 620	cag Gln	att Ile	ctg Leu	Asp	gag Glu 625	Ala	ctg Leu	aag Lys	Ile	tgc Cys 630	aac Asn	tac Tyr	4896
60	atc ttc Ile Phe 1	act Thr 635	gtc Val	atc Ile	ttt Phe	Val	ttg Leu 640	gag Glu	tca Ser	gtt Val	Phe	aaa Lys 645	ctt Leu	gtg Val	gee Ala	1944
	ttt ggt Phe Gly 1650	ttc Phe	cgt Arg	cgg Arg	Phe	tta Phe 655	cag Gln	gac Asp	agg Arg	Trp	aac Asn 660	cag Gln	ctg Leu	gac Asp	ctg Leu	4992

5	gcc att Ala Ile 1665			Leu					Ile					ĭìe	5040
	gtc aac Val Asn		Ser					Pro					Ile		5088
10	gtg ctg Val Leu	Arg					Leu					Met			5136
15	atg cgg Met Arg					Thr					Leu				5184
20	aac ctg Asn Leu 1730				Phe					Phe					5232
25	ggc gtg Gly Val 1745			P'ne					Cys					Pro	5280
	gag ggc Glu Gly		Gly					Phe					Met		. 5328
30	cta acc Leu Thr	Leu					Thr					Asn			5376
35	aag gac Lys Asp					Cys					Thr				5424
40	gtc atc Val Ile 1810				Tyr					Val					5472
45	gtg cta Val Leu 1825			Val					Leu					Glu	5520
	agc aac Ser Asn		Glu					Ala					Glu		5568
50	ctg gag Leu Glu	Met					Pro					Pro			5616
55	ccc ttc Pro Phe					Val					Ser				5664
60	aag cct Lys Pro 1890				His					Ala					5712
	ttt tcc Phe Ser 1905			His					Pro					Leú	5760

<i>5</i>	gga cca Gly Pro	gac Asp	Leu	ctg Leu 1925	act Thr	gtg Val	cgg Arg	Lys	tct Ser 1930	'GJÀ	gtc Val	ser	cga Arg	acg Thr 1935	cac His	5808
	tot otg Ser Leu	Pro	aat Asn 1940	gac Asp	ago Ser	tac Tyr	Met	tgt Cys 1945	Arg	cat His	G17 G34	Ser	act Thr 1950	gcc Ala	gag Glu	5856
10	ggg ccc Gly Pro	ctg Leu 1955	gga Gly	cac His	agg Arg	Gly	tgg Trp 1960	G] À ààà	ctc Leu	ccc	Lys	got Ala 1965	cag Gln	tca Ser	ggc Gly	5904
15	tcc gtc Ser Val 1970	Leu	tcc Ser	gtt Val	${\tt His}$	tcc Ser 1975	cag Gln	cca Pro	gca Ala	Asp	acc Thr 1980	agc Ser	tac. Tyr	atc Ile	ctg Leu	5952
20	cag ctt Gln Leu 1985	ccc Pro	aaa Lys	Asp	gca Ala 1990	cct Pro	cat His	ctg Leu	Leu	cag Gln 1995	ccc Pro	cac His	agc Ser	Āla	cca Pro 2000	6000
25	acc tgg Thr Trp	ggc	Thr	atc Ile 2005	ccc Pro	aaa Lys	ctg Leu	Pro	cca Pro 2010	cca Pro	gga Gly	ege Arg	Ser	cct Pro 2015	ttg Leu	6048
	gct cag Ala Gln	Arg	cca Pro 2020	ctc Leu	agg Arg	cgc Arg	Gln	gca Ala 2025	gca Ala	ata Ile	agg Arg	Thr	gac Asp 2030	tcc Ser	ttg Leu	6096
30	gac gtt Asp Val	cag Gln 2035	ggt Gly	ctg Leu	ggc Gly	Ser	cgg Arg 2040	gaa Glu	gac Asp	ctg Leu	Leu	gca Ala 2045	gag Glu	gtg Val	agt Ser	6144
35	ggg ccc Gly Pro 2050	Ser	ccg. Pro	ccc Pro	Leu	gcc Ala 2055	cgg Arg	gcc Ala	tac Tyr	Ser	ttc Phe 2060	tgg Trp	ggc Gly	cag Gln	tca Ser	6192
40	agt acc Ser Thr 2065	cag Gln	gca Ala	Gln	cag Gln 1070	cac His	tcc Ser	cgc Arg	Ser	cac His 2075	agc Ser	aag Lys	atc Ile	Ser	aag Lys 2080	6240
<i>45</i>	cac atg His Met	acc Thr	Pro	cca Pro 2085	gcc Ala	cct Pro	tgc Cys	Pro	Gly Ggc	cca Pro	gaa Glu	ccc Pro	Asn	tgg Trp 2095	ggc Gly	6288
	aag ggc Lys Gly	Pro	cca Pro	gag Glu	acc Thr	aga Arg	Ser	agc Ser 105	tta Leu	gag Glu	ttg Leu	qzA	acg Thr 2110	gag Glu	ctg Leu	6336
50	agc tgg Ser Trp	att Ile 2115	tca Ser	gga Gly	gac Asp	Leu	ctg Leu 120	cçc Pro	cct Pro	ggc Gly	Gly	cag Gln 125	gag Glu	gag Glu	ccc Pro	6384
<i>55</i>	cca tcc Pro Ser 2130	cca Pro	cgg Arg	gac Asp	Leu	aag Lys 135	aag Lys	tgc Cys	tac Tyr	Ser	gtg Val 2140	gag Glu	gcc Ala	cag Gln	agc Ser	6432
60	tgc cag Cys Gln 2145	cgc Arg	cgg Arg	Pro	acg Thr 150	tcc Ser	tgg Trp	ctg Leu	Asp	gag Glu 155	cag Gln	agg Arg	aga Arg	His	tot Ser 160	6480
	atc gcc Ile Ala	gtc Val,	Ser	tgc Cys 165	atg Leu	gac Asp	agc Ser	Gly	tcc Ser 170	caa Gln	Pro Pro	cac His	Leu	ggc Gly 175	aca Thr	6528

ĵ	gac cc Asp Pr	o tot o Ser	aac Asn 2180	Leu	ggg Gly	ggc	Gln	cct Pro 2185	Leu	G1% aaa	G1Ā āāā	Pro	999 Gly 2190	Ser	egg Arg	5576
J	ccc aa Pro Ly	g aaa s Lys 2195	Lys	ctc Leu	agc Ser	Pro	cct Pro 2200	agt Ser	atc Ile	acc Thr	Ile	gac Asp 2205	Pro	Pro	gag Glu	6624
10	agc cas Ser Gli 2210	n Gly	cct Pro	egg Arg	Thr	ccg Pro 2215	ccc Pro	agc Ser	cct Pro	Gly	atc Ile 2220	tgc Cys	ctc Leu	egg Arg	agg Arg	6672
15	agg gc Arg Ala 2225	cog Pro	tcc Ser	Ser	gac Asp 2230	Ser	aag Lys	gat Asp	Pro	ttg Leu 2235	gcc Ala	tot Ser	ggc Gly	Pro	cct Pro 2240	6720
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, 0	cgg ago Arg Ser	ttc Phe	atg Met 20	cgg Arg	ctc Leu	aac Asn	gac Asp	ctg Leu 25	tcg Ser	ggg Gly	gcc Ala	Gly ggg	ggg Gly 30	cgg Arg	ccg Pro	96
45	ggg ccc Gly Pro	ggg Gly 35	tca Ser	gca Ala	gaa Glu	aag Lys	gac Asp 40	ccg Pro	ggc Gly	agc Ser	gcg Ala	gac Asp 45	tcc Ser	gag Glu	gcg Ala	144
50	gag ggg Glu Gly 50	Leu	ccg Pro	tac Tyr	ccg Pro	gcg Ala 55	ctg Leu	gcc Ala	ccg Pro	gtg Val	gtt Val 60	ttc Phe	ttc Phe	tac Tyr	ttg Leu	192
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- -	acc ctg Thr Leu	ggc Gly	atg Met 100	ttc Phe	cgg Arg	cca Pro	tgc Cys	gag Glu 105	gac Asp	atc Ile	gcc Ala.	tgt Cys	gac Asp 110	tee Ser	cag Gln	336

	cgc Arg	tgc Cys	cgg Arg 115	ato Ile	otg Leu	cag Gln	gcc Ala	ttt Phe 120	gat Asp	gas gas	ttc Phe	atc Ile	ttt Phe 125	gcc Ala	ttc Phe	ttt Phe	364
5															GļĀ āāā		432
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υυ	ctg Leu	gag Glu	ggc Gly 355	tgg Trp	gtc Val	gac Asp	atc Ile	atg Met 360	tac Tyr	ttt Phe	gtg Val	atg Met	gat Asp 365	gct Ala	cat His	tcc Ser	1104

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	gcc Ala	att Ile	ctg Leu	gtg Val	gag Glu 965	ggć Gly	ttc Phe	cag Gln	gcg Ala	gag Glu 970	gga Gly	gat Asp	gcc Ala	aac Asn	aag Lys 975	tcc Ser	2928
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10								got toa Ala Ser		3552
15				g Pro		Pro		gat ggg Asp Gly		3600
20								gto ogo Val Arg		. 3648.
			g Leu Pr			s Leu		gac tcc Asp Ser 1230	tgg tca Trp Ser	3696
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30								gtc atc Val Ile		3792
35				e Ala		ı Arg		att gac Ile Asp		3840.
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55				e Leu		: Leu		ctg cgg Leu Arg		4080
60								cag ggg Gln Gly		4128
00			u Thr Le			Leu		atc ggc Ile Gly 1390		4176

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	ctg atg Leu Met 1810	aag c Lys H	ac ctg is Leu	Glu (gag Glu 815	agc Ser	aac Asn	aag Lys	Glu	gcc Ala 820	aag Lys	gag Glu	gag Glu	gcc Ala	5472
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		2000														
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	Ser His 2050 ggc cca Gly Pro 2065 tta gag	agc Ser gaa Glu ttg Leu ggc Gly	CCC Pro	aac Asn 2 acg Thr 085 gag Glu	Ser 2 tgg Trp 070 gag Glu gag	Lys 055 ggc Gly ctg Leu	His aag Lys agc Ser cca Pro	Met ggc Gly tgg Trp 2	Thr cct Pro att Ile 2090 cca	Pro cca Pro 2075 tca Ser	Pro 2060 gag Glu gga Gly	Ala acc Thr gac Asp	Pro aga Arg ctc Leu aag	Cys agc Ser ctg Leu 2095	Pro agc Ser 2080 ccc Pro tgc	6240
45	Ser His 2050 ggc cca Gly Pro 2065 tta gag Leu Glu cct ggc Pro Gly tac agc Tyr Ser	agc Ser gaa Glu ttg Leu ggc Gly 2	ccc Pro A	aac Asn 2 acg Thr 085 gag Glu	Ser 2 tgg Trp 070 gag Glu gag Glu cag	Lys 055 ggc Gly ctg Leu ccc Pro	His aag Lys agc Ser cca Pro	Met ggc Gly tgg Trp tcc Ser 2105 cag	Thr cct Pro att Ile 2090 cca Pro	Pro CCa Pro 2075 tca Ser Cgg Arg	Pro 2060 gag Glu gga Gly gac Asp	Ala acc Thr gac Asp ctg Leu acg	Pro aga Arg ctc Leu aag Lys 2110	ctg Leu 2095 aag Lys	Pro agc Ser 2080 ccc Pro tgc Cys	6240
45 50	Ser His 2050 ggc cca Gly Pro 2065 tta gag Leu Glu cct ggc Pro Gly tac agc Tyr Ser	agc Ser gaa Glu ttg Leu ggc Gly 2 gtg Val 2115 cag	ccc Pro A gac Asp 2 cag Gln 100 gag Glu A agg	aac Asn 2 acg Thr 085 gag Glu gcc Ala	Ser 2 tgg Trp 070 gag Glu gag Glu cag Gln cac His	Lys 055 ggc Gly ctg Leu ccc Pro agc Ser 2	Aag Lys agc Ser cca Pro tgc Cys	Met ggc Gly tgg Trp tcc Ser 2105 cag Gln	Thr cct Pro att Ile 2090 cca Pro cgc Arg	Pro CCa Pro 2075 tca Ser Cgg Arg	Pro 2060 gag Glu gga Gly gac Asp	Ala acc Thr gac Asp ctg Leu acg Thr 125	Pro aga Arg ctc Leu aag Lys 110 tcc Ser	Cys agc Ser ctg Leu 2095 aag Lys tgg Trp	Pro agc Ser 2080 ccc Pro tgc Cys ctg Leu ggc	6240 6288 6336

	ctt Leu	GJ À aàa	ggg Gly	Pro	999 Gly 2165	agc Ser	cgg Arg	SEC	Lys	aaa Lys 2170	aaa Lys	ctc Leu	agc Ser	Pro	cct Pro 2175	ag: Ser	6523
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45	ggg Gly	ccg												50			
	•	Pro	Gly 35	tcg Ser	acg Thr	gaa Glu	aag Lys	gac Asp 40	ccg Pro	ggc Gly	agc Ser	gcg Ala	gac Asp 45	tcc	gag Glu	gcg Ala	. 144
50	gag	Pro ggg	Gly -35 ctg	Ser	Thr	Glu	Lys	Asp 40 cta	Pro gcc	ggc Gly ccg Pro	Ser gtg	Ala	Asp 45 ttc	tcc Ser	Glu	Ala	192
50	gag Glu agc	ggg Gly 50	Gly -35 ctg Leu gac	Ser ccg Pro	Thr tac Tyr	Glu ccg Pro	gcg Ala 55	Asp 40 cta Leu	Pro gcc Ala	Gly	Ser gtg Val	Ala gtt Val 60 cgc	Asp 45 ttc Phe acg	tcc Ser ttc Phe	Glu tac Tyr	Ala ttg Leu	· .
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	gag Glu agc Ser 65 ccg Pro	Pro ggg Gly 50 cag Gln tgg Trp	Gly 35 ctg Leu gac Asp ttc Phe	Ser ccg Pro agc Ser gag Glu atg	Thr tac Tyr cgc Arg cga Arg 85 ttc	Glu ccg Pro ccg Pro 70 gtc Val	Lys gcg Ala 55 cgg Arg agt Ser	Asp 40 cta Leu agc Ser atg Met	Pro gcc Ala tgg Trp ctg Leu gag	ccg Pro tgt Cys	Ser gtg Val ctc Leu 75 att Ile	Ala gtt Val 60 cgc Arg ctt Leu gcc	Asp 45 ttc Phe acg Thr ctc Leu	tcc Ser ttc Phe gtc Val aac Asn	tac Tyr tgt Cys tgt Cys 95	Ala ttg Leu aac Asn 80 gtg Val cag	192

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10	aaa Lys 145	tgt Cys	tac Tyr	ctg Leu	gga Gly	gac Asp 150	act Thr	tgg Trp	aac Asn	cgg Arg	ctt Leu 155	gac Asp	ttt Phe	ttc Phe	att Ile	gtc Val 160	480
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35								gag Glu									816
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45	cgt Arg	ggg Gly 290	gaa Glu	ggc Gly	ggt Gly	ggt Gly	ggc Gly 295	cca Pro	ccc Pro	tgc Cys	agt Ser	ctg Leu 300	gac Asp	tat Tyr	gag Glu	acc Thr	912
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								cac His									1008
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10						acc Thr											1296
15						aag Lys											1344
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25						gcc Ala 470										ggc Gly 480	1440
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30						cat His											1536
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	tcg Ser	gag Glu	gca Ala	tct Ser 580	ggt Gly	agg Arg	act Thr	gtg Val	ggt Gly 585	agt Ser	GJA āāā	aag Lys	gtg Val	tac Tyr 590	ccc Pro	act Thr	1776
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age ate etg gge atg cat etc tit ggt tge aag tte gea tet gaa egg

Ser Ile Leu Gly Met His Leu Phe Gly Cys Lys Phe Ala Ser Glu Arg

2688

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10	gcc.at Ala Il		l Thr													2784
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15	ttc at Phe Il 945															2880
20	gtg go Val Al															2928
25	tct ga Ser Gl															2976
30	gac ac Asp Ar		Lys	_	_	Āla	_		-	_	Ğĺy	_			_	3024
	cta co Leu Ar 101	g Ly			Leu					Ile						3072
35	cca at Pro Me 1025			Pro					Thr					Ala		3120
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45	gct gc Ala Al						Cys					Arg				3216
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	cat cg His Ar															3456

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						tgc Cys											4224

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	atg cgg Met Arg	gca ctg ct Ala Leu Le 1700	ig cac acg eu His Thr	gtg atg Val Met 1705	cag gcc ct Gln Ala Le	g ccc cag gtg eu Pro Gln Val 1710	ggg 5136 Gly
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40	cgt ag Arg Se	c ttc r Phe	acg Thr 20	cag Gln	ctc Leu	aac Asn	gac Asp	ctg Leu 25	tcc Ser	GJ À ààà	gcc Ala	Gly ggg	ggc 30	cgg Arg	cag Gln	96
45	ggg co Gly Pr	g ggg o Gly 35	tcg Ser	acg Thr	gaa Glu	aag Lys	gac Asp 40	ccg Pro	ggc Gly	agc Ser	gcg Ala	gac Asp 45	tcc Ser	gag Glu	gcg Ala	144
	gag gg Glu Gl	g ctg y Leu 0	ccg Pro	tac Tyr	ccg Pro	gcg Ala 55	cta Leu	gcc Ala	ccg Pro	gtg Val	gtt Val 60	ttc Phe	ttc Phe	tac Tyr	ttg Leu	192
50	agc ca Ser Gl 65	ig gac .n Asp	agc Ser	cgc Arg	ccg Pro 70	cgg Arg	agc Ser	tgg Trp	tgt Cys	ctc Leu 75	cgc Arg	acg Thr	gtc Val	tgt Cys	aac Asn 80	240
<i>35</i>	ccg tg Pro Tr															288
60	act ct Thr Le	g ggt u Gly	atg Met 100	Phe	agg Arg	ccg Pro	tgt Cys	gag Glu 105	gac Asp	att Ile	gcc Ala	tgt Cys	gac Asp 110	tcc Ser	cag Gln	336
	cgc to Arg Cy	jc cgg /s Arg 115	atc Ile	ctg Leu	cag Gln	gcc Ala	ttc Phe 120	gat Asp	gac Asp	ttc Phe	atc Ile	ttt Phe 125	gcc Ala	ttc Phe	ttt Phe	384

5	gct Ala	gtg Val 130	gaa Glu	atg Met	gtg Val	gtg Val	aag Lys 135	atg Met	gtg Val	gcc Ala	ttg Leu	ggc Gly 140	atc Ile	ttt Phe	Gly ggg	aag Lys	432
J	aaa Lys 145	tgt Cys	tac Tyr	ctg Leu	gga Gly	gac Asp 150	act Thr	tgg Trp	aac Asn	cgg Arg	ctt Leu 155	gac Asp	ttt Phe	tto Phe	att Ile	gtc Val 160	480
10	att Ile	gca Ala	ggg ggg	atg Met	ctg Leu 165	gag Glu	tat Tyr	tog Ser	ctg Leu	gac Asp 170	ctg Leu	cag Gln	aac Asn	gtc Val	agc Ser 175	ttc Phe	528
15				agg Arg 180													576
20				agc Ser													624
25	cct Pro	atg Met 210	ctg Leu	ggc Gly	aac Asn	gtc Val	ctg Leu 215	ctg Leu	ctc Leu	tgt Cys	ttc Phe	ttc Phe 220	gtc Val	ttt Phe	ttc Phe	atc Ile	672
	ttt Phe 225	ggc Gly	atc Ile	gtg Val	ggc Gly	gtc Val 230	cag Gln	ctg Leu	tgg Trp	gca Ala	gga Gly 235	ctg Leu	ctt Leu	cgc Arg	aac Asn	cgg Arg 240	720
30				ccc Pro													768
35	cct Pro	tat Tyr	tac Tyr	cag Gln 2 <u>6</u> 0	aca Thr	gag Glu	aat Asn	gag Glu	gac Asp 265	gag Glu	agc Ser	ccc Pro	ttc Phe	atc Ile 270	tgc Cys	tct Ser	816
40	cag Gln	cct Pro	cgg Arg 275	gag Glu	aat Asn	ggc Gly	atg Met	aga Arg 280	tcc Ser	tgc Cys	agg Arg	agt Ser	gtg Val 285	ccc Pro	aca Thr	ctg Leu	864
45	cgt Arg	ggg Gly 290	gaa Glu	ggc Gly	ggt Gly	ggt Gly	ggc Gly 295	cca Pro	ccc Pro	tgc Cys	agt Ser	ctg Leu 300	gac Asp	tat Tyr	gag Glu	acc Thr	.912
	tat Tyr 305	aac Asn	agt Ser	tcc Ser	agc Ser	aac Asn 310	acc Thr	acc Thr	tgt Cys	gtc Val	aac Asn 315	tgg Trp	aac Asn	cag Gln	tac Tyr	tat Tyr 320	960
50	acc Thr	aac Asn	tgc Cys	tct Ser	gcg Ala 325	ggc Gly	gag Glu	cac His	aac Asn	ccc Pro 330	ttc Phe	aaa Lys	ggc Gly	gcc Ala	atc Ile 335	aac Asn	1008
55	ttt Phe	gac Asp	aac Asn	att Ile 340	ggc Gly	tat Tyr	gcc Ala	tgg Trp	atc Ile 345	gcc Ala	atc Ile	ttc Phe	cag Gln	gtc Val 350	atc Ile	aca Thr	1056
60	ctg Leu	gag Glu	ggc Gly 355	tgg Trp	gtc Val	gac Asp	atc Ile	atg Met 360	tac Tyr	ttc Phe	gta Val	atg Met	gac Asp 365	gct Ala	cac His	tcc . Ser	1104
				ttc Phe													1152

<i>5</i>			atc Ile														1200
2			cag Gln													ttc Phe	1248
10	ctg Leu	tcc Ser	aat Asn	gct Ala 420	agc Ser	acc Thr	ctg Leu	gca Ala	agc Ser 425	ttc Phe	tct Ser	gag Glu	cca Pro	ggc Gly 430	agc Ser	tgc Cys	1296
15	tat Tyr	gag Glu	gag Glu 435	cta Leu	ctc Leu	aag Lys	tac Tyr	ctg Leu 440	gtg Val	tac Tyr	atc Ile	ctc Leu	cga Arg 445	aaa Lys	gca Ala	gcc Ala	1344
20	cga Arg	agg Arg 450	ctg Leu	gcc Ala	cag Gln	gtc Val	tct Ser 455	agg Arg	gct Ala	ata Ile	Gly	gtg Val 460	cgg Arg	gct Ala	ggg Glý	ctg Leu	1392
25	ctc Leu 465	agc Ser	agc Ser	cca Pro	gtg Val	gcc Ala 470	cgt Arg	agt Ser	Gly	cag Gln	gag Glu 475	ccc Pro	cag Gln	ccc Pro	agt Ser	ggc Gly 480	1440
			act Thr														1488
30			cac His														1536
35			ccc Pro 515														1584
40			cgg Arg														1632
45			ccg Pro														1680
			ttg Leu														1728
50			gca Ala														1776
55	gtg Val	cat His	acc Thr 595	agc Ser	cct Pro	cca Pro	cca Pro	gag Glu 600	ata Ile	ctg Leu	aag Lys	gat Asp	aaa Lys 605	gca Ala	cta Leu	gtg Val	1824
60			gcc Ala														1872
	cca Pro 625	cct Pro	ggg Gly	ccc Pro	ttc Phe	agc Ser 630	tcc Ser	atg Met	cac His	aag Lys	ctc Leu 635	ctg. Leu	gag Glu	aca Thr	cag Gln	agt Ser 640	1920

ĵ	acq Thi	Gl;	a gcc / Ala	tgo Cys	cat His 645	: Ser	toc Ser	tg: Cys	aaa Lys	ato 11e 650	Se:	c ago c Ser	oct	t tg: D Cys	5 E C S 5 Se 1 65 S	aag Lys	1968
	gca Ala	gad Asp	agt Ser	660 660	/ Ala	tgc Cys	: ggg	r Ccq	gac Asp 665	Ser	tgt Cys	ccc Pro	tac Tyr	tgt Cys 670	Ala	c cgg a Arg	2016
10	aca Thr	gga Gly	gca Ala 675	Gly	gag Glu	cca Pro	gag Glu	Ser 680	Ala	gac	cat His	gtc Val	: ang : Met : 685	Pro	gac Asp	tca Ser	2064
15	gac Asp	ago Ser 690	GLu	gct Ala	gtg Val	tat Tyr	gag Glu 695	Phe	aca Thr	cag Gln	gac Asp	gct Ala 700	Gln	cac His	agt Ser	gac	2112
20	ctc Leu 705	Arg	gat Asp	çcc Pro	cac Ĥis	agc Ser 710	cgg Arg	cgg Arg	cga Arg	cag Gln	cgg Arg 715	Ser	ctg Leu	GŢ Ā ādc	cca Pro	gat Asp 720	2160
25	gca Ala	gag Glu	cct Pro	agt Ser	tct Ser 725	gtg Val	ctg Leu	gct Ala	ttc Phe	tgg Trp 730	agg Arg	ctg Leu	atc Ile	tgt Cys	gac Asp 735	Thr	2208
	ttc Phe	cgg Arg	aag Lys	atc Ile 740	gta Val	gat Asp	agc Ser	aaa Lys	tac Tyr 745	ttt Phe	ggc	cgg Arg	gga Gly	atc Ile 750	atg Met	atc Ile	2256
·30	gcc Ala	atc Ile	ctg Leu 755	Val	aat Asn	aca Thr	ctc Leu	agc Ser 760	atg Met	ggc Gly	atc Ile	gag Glu	tac Tyr 765	cac His	gag Glu	cag Gln	2304
35	ccc Pro	gag Glu 770	gag Glu	ctc Leu	acc Thr	aac Asn	gcc Ala 775	ctg Leu	gaa Glu	atc Ile	agc Ser	aac Asn 780	atc Ile	gtc Val	ttc Phe	acc Thr	2352
40	agc Ser 785	ctc Leu	ttc Phe	gcc Ala	ttg Leu	gag Glu 790	atg Met	ctg Leu	ctg Leu	aaa Lys	ctg Leu 795	ctt Leu	gtc 'Val	tac Tyr	ggt Gly	ccc Pro 800	2400
<i>45</i>	ttt Phe	ggc Gly	tac Tyr	att Ile	aag Lys 805	aat Asn	ccc Pro	tac Tyr	aac Asn	atc Ile 810	ttt Phe	gat Asp	ggt Gly	gtc Val	att Ile 815	gtg Val	2448
	gtc Val	atc Ile	agt Ser	gtg Val 820	tgg Trp	gag Glu	att Ile	gtg Val	ggc Gly 825	cag Gln	cag Gln	gga Gly	ggt Gly	ggc Gly 830	ctg Leu	tcg Ser	2496
50	gtg Val	ctg Leu	cgg Arg 835	acc Thr	ttc Phe	cgc Arg	ctg Leu	atg Met 840	cgg Arg	gtg Val	ctg Leu	aag Lys	ctg Leu 845	gtg Val	cgc Arg	ttc Phe	2544
55	ctg Leu	.ccg Pro 850	gcc Ala	ctg Leu	cag Gln	cgc Arg	cag Gln 855	ctc Leu	gtg Val	gtg Val	ctc Leu	atg Met 860	aag Lys	acc Thr	atg Met	gac Asp	2592
60	aac Asn 865	gtg Val	gcc Ala	acc Thr	Phe	tgc Cys 870	atg. Met	ctc Leu	ctc Leu	atg Met	ctg Leu 875	ttc Phe	atc Ile	ttc Phe	atc	ttc Phe 880	2640
٠	agc Ser	atc Ile	ctg Leu	ggc Gly	atg Met 885	cat His	ctc Leu	ttt Phe	ggt Gl.y	tgc Cys 890	aag Lys	ttc Phe	gca Ala	tct Ser	gaa Glu 895	cgg Arg	2688

<i>5</i>					ttg Leu												2736
	gcc Ala	atc Ile	gtc Val 915	act Thr	gtc Val	ttt Phe	cag Gln	att Ile 920	ctg Leu	act Thr	cag Gln	gaa Glu	gac Asp 925	tgg Trp	aat Asn	aaa Lys	2784
10	gtc Val	ctc Leu 930	tac Tyr	aac Asn	ggc Gly	atg Met	gcc Ala 935	tcc Ser	aca Thr	tcg Ser	tct Ser	tgg Trp 940	gct Ala	got Ala	ctt Leu	tac Tyr	2832
<i>15</i>	ttc Phe 945	ātc Ile	gcc Ala	ctc Leu	atg Met	act Thr 950	ttt Phe	ggc Gly	aac Asn	tat Tyr	gtg Val 955	ctc Leu	ttt Phe	aac Asn	ctg Leu	ctg Leu 960	2880
20					gtg Val 965												2928
25	tct Ser	gag Glu	tca Ser	gag Glu 980	cct Pro	gat Asp	ttc Phe	ttt Phe	tcg Ser 985	ccc Pro	agt Ser	gtg Val	gat Asp	990 Gly. ggt	gat Asp	ggg Gly	2976
					cgc Arg		Ala					Gly					3024
30	Leu				ctt Leu	Leu					Ile						3072
35	cca Pro 1025	Met	tca Ser	cac His	ccc Pro	aag Lys .030	agc Ser	tcc Ser	agc' Ser	Thr	ggt Gly 1035	gtg Val	ggg Gly	gaa Glu	Ala	ctg Leu 1040	3120
40				Ser	cga Arg 1045				Ser					Glu			3168
45	gct Ala	gcc Ala	His	cat His 1060	gag Glu	atg Met	aaa Lys	Cys	ccg Pro 1065	cca Pro	agt Ser	gcc Ala	Arg	agc Ser .070	tcc Ser	ccg Pro	3216
		Ser			agt Ser		Ala					Ser					3264
50	Arg				ggc Gly	Arg					Lys						3312
55		Glu			tcc Ser					Glu					Gln		3360
60				Ser	tca Ser 1125				Arg					Gly			3408
	cat His	cgc Arg	His	agg Arg 1140	ggt Gly	tcc Ser	ttg Leu	Glu	cgt Arg 1145	gag Glu	gcc Ala	aag Lys	Ser	tcc Ser L150	ttt Phe	gac Asp	3456

5	ctg cot gad act ctg dag gtg dog ggg dtg dad dgd ada god agd ggd Leu Pro Asp Thr Leu Gln Val Pro Gly Leu His Arg Thr Ala Ser Gly 1155 1160 1165	3504
	cgg ago tot ged tot gag cao caa gad tgt aat ggd aag tog got toa Arg Ser Ser Ala Ser Glu His Gin Asp Cys Asn Gly Lys Ser Ala Ser 1170 1175 1180	3552
10	ggg cgt ttg gcc cgc acc ctg agg act gat gac ccc caa ctg gat ggg Gly Arg Leu Ala Arg Thr Leu Arg Thr Asp Asp Pro Gln Leu Asp Gly 1185 1200	3600
15	gat gat gac aat gat gag gga aat ctg agc aaa ggg gaa cgc ata caa Asp Asp Asp Asn Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Ile Gln 1205 1210 1215	3648
20	gcc tgg gtc aga tcc cgg ctt cct gcc tgt tgc cga gag cga gat tcc Ala Trp Val Arg Ser Arg Leu Pro Ala Cys Cys Arg Glu Arg Asp Ser 1220 1225 1230	3696
25	tgg tcg gcc tat atc ttt cct cct cag tca agg ttt cgt ctc ctg tgt Trp Ser Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Cys 1235 1240 1245	3744
٠.	cac cgg atc atc acc cac aag atg ttt gac cat gtg gtc ctc gtc atc His Arg Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile 1250 1250	3792
.30	atc ttc ctc aac tgt atc acc atc gct atg gag cgc ccc aaa att gac Ile Phe Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp 1265 1270 1275 1280	3840
35	ccc cac agc gct gag cgc atc ttc ctg acc ctc tcc aac tac atc ttc Pro His Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe 1285 1290 1295	3888
40	acg gca gtc ttt cta gct gaa atg aca gtg aag gtg gtg gca ctg ggc Thr Ala Val Phe Leu Ala Glu Met Thr Val Lys Val Val Ala Leu Gly 1300 1305	3936
45	tgg tgc ttt ggg gag cag gcc tac ctg cgc agc agc tgg aat gtg ctg Trp Cys Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu 1315 1320	3984
	gac ggc ttg ctg gtg ctc atc tcc gtc atc gac atc ctg gtc tcc atg Asp Gly Leu Leu Val Leu Ile Ser Val Ile Asp Ile Leu Val Ser Met 1330 1335 1340	4032
50	gtc tcc gac agc ggc acc aag atc ctt ggc atg ctg agg gtg ctg cgg Val Ser Asp Ser Gly Thr Lys Ile Leu Gly Met Leu Arg Val Leu Arg 1345 1350 1355	4080
55	ctg ctg cgg acc ctg cgt cca ctc agg gtc atc agc cgg gcc cag gga Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Gln Gly 1375	4128
60	ctg aag ctg gtg gta gag act ctg atg tca tcc ctc aaa ccc att ggc Leu Lys Leu Val Val Glu Thr Leu Met Ser Ser Leu Lys Pro Ile Gly 1380 1385	4176
	aac att gtg gtc att tgc tgt gcc ttc ttc atc att ttt gga att ctc Asn Ile Val Val Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu 1395 1400 1405	4224

5	ggg gtg cag ctc ttc aaa ggg aag ttc ttc gtg tgt cag ggt gag gac Gly Val Gln Leu Phe Lys Gly Lys Phe Phe Val Cys Gln Gly Glu Asp 1410 1415 1420	4272
-	acc agg aac atc act aac aaa too gac tgo got gag goo ago tao oga Thr Arg Asn Ile Thr Asn Lys Ser Asp Cys Ala Glu Ala Ser Tyr Arg 1425 1430 1435 1440	4320
10	tgg gtc cgg cac aag tac aac ttt gac aac ctg ggc cag gct ctg atg Trp Val Arg His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met 1445 1450 1455	4368
15	tcc ctg ttt gtg ctg gcc tcc aag gat ggt tgg gtt gac atc atg tat Ser Leu Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr 1460 1465 1470	4416
20	gat ggg ctg gat gct gtg ggt gtg gat cag cag ccc ate atg aac cac Asp Gly Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His 1475 1480 1485	4464
25	aac ccc tgg atg ctg cta tac ttc atc tcc ttc ctc ctc atc gtg gcc Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ala 1490 1495 1500	4512
23	ttc ttt gtc ctg aac atg ttt gtg ggc gtg gtg gtg gag aac ttc cat Phe Phe Val Leu Asn Met Phe Val Gly Val Val Glu Asn Phe His 1505 1510 1515 1520	4560
30	aag tgc aga cag cac cag gag gag gag gag gcg agg cgg c	4608
35	aag cga cta cgg agg ctg gag aaa aag aga agg aat cta atg ttg gac Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg Asn Leu Met Leu Asp 1540 1545 1550	4656
40	gat gta att gct tcc ggc agc tca gcc agc gct gcg tca gaa gcc cag Asp Val Ile Ala Ser Gly Ser Ser Ala Ser Ala Ala Ser Glu Ala Gln 1555 1560 1565	4704
45	tgc aag ccc tac tac tct gac tac tcg aga ttc cgg ctc ctt gtc cac Cys Lys Pro Tyr Tyr Ser Asp Tyr Ser Arg Phe Arg Leu Leu Val His 1570 1575 1580	4752
	cac ctg tgt acc agc cac tac ctg gac ctc ttc atc act ggt gtc atc His Leu Cys Thr Ser His Tyr Leu Asp Leu Phe Ile Thr Gly Val Ile 1585 1590 1595 1600	4800
50	ggg ctg aac gtg gtc act atg gcc atg gaa cat tac cag cag ccc cag Gly Leu Asn Val Val Thr Met Ala Met Glu His Tyr Gln Gln Pro Gln 1605 1610 1615	4848
55	atc ctg gac gag gct ctg aag atc tgc aat tac atc ttt acc gtc atc Ile Leu Asp Glu Ala Leu Lys Ile Cys Asn Tyr Ile Phe Thr Val Ile 1620 1625 1630	4896
60	ttt gtc ttt gag tca gtt ttc aaa ctt gtg gcc ttt ggc ttc cgc cgt Phe Val Phe Glu Ser Val Phe Lys Leu Val Ala Phe Gly Phe Arg Arg 1635 1640 1645	4944
	ttc ttc cag gac agg tgg aac cag ctg gac ctg gct att gtg ctt ctg Phe Phe Gln Asp Arg Trp Asn Gln Leu Asp Leu Ala Ile Val Leu Leu 1650 1655 1660	4992

5			Leu Glu Glu	att gag gtc a Ile Glu Val A 1675	Asn Leú Ser	
	ccc atc aac Pro Ile Asn	ccc acc atc Pro Thr Ile 1685	Ile Arg Ile	atg agg gtg o Met Arg Val 1 1690	etc ege att Leu Arg Ile 1695	gct 5088 Ala
10	cga gtt ctg Arg Val Leu	aag ctg ttg Lys Leu Leu 1700	aag atg gct Lys Met Ala 1705	gtg ggc atg o Val Gly Met <i>I</i>	egg gca ctg Arg Ala Leu 1710	ctg 5136 Leu
15	cac acg gtg His Thr Val 1715	Met Gln Ala	ctg ccc cag Leu Pro Gln 1720	gtg ggg aac o Val Gly Asn I	etg gga ctt Leu Gly Leu 725	ctc 5134 Leu
20	ttc atg tta Phe Met Leu 1730	Leu Phe Phe	atc ttt gca Ile Phe Ala 1735	gct ctg ggc o Ala Leu Gly V 1740	gtg gag ctc /al Glu Leu	ttt 5232 Phe
<i>25</i>	gga gac ctg Gly Asp Leu 1745	gag tgt gat Glu Cys Asp 1750	Glu Thr His	cct tgt gag c Pro Cys Glu C 1755	Sly Leu Gly	cgg 5280 Arg 760
•	cat gcc acc His Ala Thr	ttt agg aac Phe Arg Asn 1765	Phe Gly Met	gcc ttt ctg a Ala Phe Leu 1 1770	acc ctc ttc Thr Leu Phe 1775	cga 5328 Arg
30	Val Ser Thr			att atg aag g Ile Met Lys A		
35	Asp Cys Asp 1795	Gln Glu Ser	Thr Cys Tyr 1800		le Ser Pro	Ile
40	tac ttt gtg Tyr Phe Val 1810	Ser Phe Val	ctg acg gcc Leu Thr Ala 1815	cag ttt gtg c Gln Phe Val I 1820	etg gtc aac weu Val Asn	gtg 5472 Val
45.	Val Ile Ala 1825	Val Leu Met 1830	Lys His Leu	gaa gaa agc a Glu Glu Ser A 1835	isn Lys Glu l	Ala 840
	aag gag gag Lys Glu Glu	gcc gag ctc Ala Glu Leu 1845	Glu Ala Glu	ctg gag ctg g Leu Glu Leu G 1850	ag atg aag lu Met Lys 1855	acg 5568 Thr
50	Leu Ser Pro			ggc agc ccc t Gly Ser Pro F		
5 5	ggg gtg gag Gly Val Glu 1875	ggt gtc aac Gly Val Asn	agt act gac Ser Thr Asp 1880	agc cct aag c Ser Pro Lys F 18	ct ggg gct ro Gly Ala 85	cca 5664 Pro
60	cac acc act His Thr Thr 1890	Ala His Ile	gga gca gcc Gly Ala Ala 1895	tcg ggc ttc t Ser Gly Phe S 1900	cc ctt gag er Leu Glu	cac 5712 His
	ccc acg atg Pro Thr Met 1905	gta ccc cac Val Pro His 1910	ecc gag gag Pro Glu Glu	gtg cca gtc c Val Pro Val F 1915	ro Leu Gly	cca 5760 Pro 920

<i>5</i>	gac ctg ctg Asp Leu Leu	act gtg ag Thr Val Ar 1925	g åag tot o g Lys Ser 0	ggt gtc agc Gly Val Ser 1930	ogg acg cac Arg Thr His	tot otg 5808 Ser Leu 1935
-	Pro Asn Asp		t Cys Arg A		act gct gag Thr Ala Glu 1950	
10	cta gga cac Leu Gly His 1955	Arg Gly Tr	g ggg ctc c c Gly Leu F 1960	ccc aaa gcc Pro Lys Ala	cag toa ggo Gln Ser Gly 1965	tcc atc 5904 Ser Ile
15	ttg tcc gtt Leu Ser Val 1970	cac tcc ca His Ser Gl	a cca gca g n Pro Ala A 1975	Asp Thr Ser	tgc atc cta Cys Ile Leu 1980	cag ctt 5952 Gln Leu
20	ccc aaa gat Pro Lys Asp 1985	gtg cac ta Val His Ty: 199	r Leu Leu G	cag cct cat Gln Pro His 1995	ggg gct ccc Gly Ala Pro	acc tgg 6000 Thr Trp. 2000
25					tcc cct ctg Ser Pro Leu	
20	Arg Pro Leu	agg cgc ca: Arg Arg Gl: 2020	n Ala Ala I	ata agg act lle Arg Thr 025	gac tcc ctg Asp Ser Leu 2030	gat gtg 6096 Asp Val
30	cag ggc ctg Gln Gly Leu 2035	Gly Ser Ar	g gaa gac c g Glu Asp I 2040	ctg ttg tca Leu Leu Ser	gag gtg agt Glu Val Ser 2045	ggg ccc 6144 Gly Pro
35	tcc tgc cct Ser Cys Pro 2050	ctg acc cgo .Leu Thr Arc	g too toa t g Ser Ser S 2055	Ser Phe Trp	ggc ggg tcg Gly Gly Ser 2060	agc atc 6192 Ser Ile
40			Gly Ile G		gtc tcc aag Val Ser Lys	
45	cgc ctg cca Arg Leu Pro	gcc cct tgc Ala Pro Cys 2085	cca ggc c Pro Gly L	etg gaa ccc Leu Glu Pro 2090	agc tgg gcc Ser Trp Ala	aag gac 6288 Lys Asp 2095
	Pro Pro Glu		Ser Leu G		acg gag ctg Thr Glu Leu 2110	
50	att tca gga Ile Ser Gly 2115	Asp Leu Le	ccc agc a Pro Ser S 2120	igc cag gaa Ser Gln Glu	gaa ccc ctg Glu Pro Leu 2125	ttc cca 6384 Phe Pro
55				al Glu Thr	cag agc tgc Gln Ser Cys 2140	
60			ı Asp Glu G		cac tcc att His Ser Ile	
	agc tgt ctg Ser Cys Leu	gac agc gg Asp Ser Gl 2165	c too caa c Ser Gln F	ccc cgc cta Pro Arg Leu 2170	tgt cca agc Cys Pro Ser	ccc tca 6528 Pro Ser 2175

<u></u>	agc ctc Ser Leu	ggg g Gly G 21	ly Gln	cct Pro	ctt Leu	Gly	ggt Gly 2185	cct Pro	G17. aaa	ago Ser	Arg	pro 2190	aag Lys	aaa Lys	6576
5	aaa ctc Lys Leu 2	agc co Ser P: 195	ca ccc ro Pro	agt Ser	Ile	tct Ser 2200	ata Ile	gac Asp	ccc Pro	Pro	gag Glu 205	agc Ser	cag Gln	G]A ggc	6624
10	tct cgg Ser Arg 2210	ccc co Pro P	ca tgc ro Cys	Ser	cct Pro	ggt Gly	gtc Val	tgc Cys	Leu	agg Arg	agg Arg	agg Arg	gcg Ala	ccg Pro	6672
15	gcc agt Ala Ser 2225	gac to Asp So	er Lys	gat Asp 2230	ccc Pro	tcg Ser	gtc Val	Ser	agc Ser 235	ccc Pro	ctr Leu	gac Asp	Ser	acg Thr 2240	6720
20	gct gcc Ala Ala	tca c Ser P	cc tcc ro Ser 2245	cca Pro	aag Lys	aaa Lys	Asp	acg Thr 2250	ctg Leu	agt Ser	ctc Leu	Ser	ggt Gly 2255	ttg Leu	6768
25	tct tct Ser Ser	gac co Asp P. 22	ro Thr	gac Asp	atg Met	Asp	ccc Pro 2265								6795
25															
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	<220>														
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35	<221> CD <222> (1		816)												•
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10	aaa Lys 145	tgt Cys	tac Tyr	ctg Leu	gga Gly	gac Asp 150	act Thr	tgg Trp	aac Asn	cgg Arg	ctt Leu 155	gac Asp	ttt Phe	IIC Phe	att Tie	gtc Val 160	480
15						gag Glu											528
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30						gtc Val 230											720 .
35						aac Asn											768
40						gag Glu											816
						ggc Gly											864
45						ggt Gly											912
50	tat Tyr 305	aac Asn	agt Ser	tcc Ser	agc Ser	aac Asn 310	acc Thr	acc Thr	tgt Cys	gtc Val	aac Asn 315	tgg Trp	aac Asn	cag Gln	tac Tyr	tat Tyr 320	960
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60						tat Tyr											1056
- *						gac Asp										tcc Ser	1104

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10	acc Thr	aaa Lys	cag Gln	cgg Arg	gag Glu 405	agt Ser	cag Gln	ctg Leu	atg Met	cgg Arg 410	gag Glu	cag Gln	cgt Arg	gta Val	cga Arg 415	ttc Phe	1248
15	ctg Leu	tcc Ser	aat Asn	gct Ala 420	agc Ser	acc Thr	ctg Leu	gca Ala	agc Ser 425	ttc Phe	tct Ser	gag Glu	cca Pro	ggc Gly 430	agc Ser	tgc Cys	1296
20											atc Ile						1344
20	cga Arg	agg Arg 450	ctg Leu	gcc Ala	cag Gln	gtc Val	tct Ser 455	agg Arg	gct Ala	ata Ile	ggc Gly	gtg Val 460	cgg Arg	gct Ala	G] À aaa	ctg Leu	1392
25	ctc Leu 465	agc Ser	agc Ser	cca Pro	gtg Val	gcc Ala 470	cgt Arg	agt Ser	Gly	cag Gln	gag Glu 475	ccc Pro	cag Gln	ccc Pro	agt Ser	ggc Gly 480	1440
30	agc Ser	tgc Cys	act Thr	cgc Arg	tca Ser 485	cac His	cgt Arg	cgt Arg	ctg Leu	tct Ser 490	gtc Val	cac His	cac His	ctg Leu	gtc Val 495	cac His	1488
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40	aga Arg	gtt Val	ccc Pro 515	cgg Arg	gcc Ala	agc Ser	cca Pro	gag Glu 520	atc Ile	cag Gln	gac Asp	agg Arg	gat Asp 525	gcc Ala	aat Asn	Gly	1584
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45	ggc Gly 545	cct Pro	ccg Pro	agg Arg	ggt Gly	gcg Ala 550	gag Glu	tct Ser	gta Val	cac His	agc Ser 555	ttc Phe	tac Tyr	cat His	gct Ala	gac Asp 560	1680
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60	gtg Val	cat His	acc Thr 595	agc Ser	cct Pro	cca Pro	cca Pro	gag Glu 600	ata Ile	ctg Leu	aag Lys	gat Asp	aaa Lys 605	gca Ala	cta Leu	gtg Val	1824
UU	gag Glu	gtg Val 610	gcc Ala	ccc Pro	agc Ser	cct Pro	ggg Gly 615	ccc Pro	ccc Pro	acc Thr	ctc Leu	acc Thr 620	agc Ser	ttc Phe	aac Asn	atc Ile	1872

	cca Pro 625) Fro	Gly	g ccc	tto Phe	s ago Ser 630	Ser	atç Met	cac His	aag Lys	Leu 635	ı Leu	gag Glu	aca Thr	caç Gl:	agt Ser 640	1920
5	acg Thr	gga Gly	gco Ala	tgc Cys	cat His 645	Ser	Ser	tgc Cys	: aaa : Lys	atc Ile 650	Ser	ago Ser	cct Pro	tgc Cys	Ser 655	aag Lys	1968
10	Ата	Asp	Ser	660	Ala	Cys	Gly	Pro	Asp 665	Ser	Cys	Pro	Tyr	Cys 670	Ala	cgg Arg	2016
15	Thr	GLY	675	Gly	Glu	Pro	Glu	Ser 680	Ala	Asp	His	gtc Val	Met 685	Pro	Asp	Ser	2064
20	Asp	Ser 690	GLu	Ala	Val	Tyr	Glu 695	Phe	Thr	Gln	Asp	gct Ala 700	Gln	His	Ser	Asp	2112
2.5	705	Arg	Asp	Pro	His	Ser 710	Arg	Arg	Arg	Gln	Arg 715	agc Ser	Leu	Gly	Pro	Asp 720	2160
25	ATA	GLu	Pro	Ser	Ser 725	Val	Leu	Ala	Phe	Trp 730	Arg	ctg Leu	Ile	Cys	Asp 735	Thr	2208
30	Phe	Arg	Lys	11e 740	Val	Asp	Ser	Lys	Tyr 745	Phe	Gly	cgg Arg	Gly	11e 750	Met	Ile	2256
35	Ala	lle	155 755	Val	Asn	Thr	Leu	Ser 760	Met	Gly	Ile	gag Glu	Tyr. 765	His	Glu	Gln	2304
40	Pro	770	Glu	Leu	Thr	Asn	Ala 775	Leu	Glu	Ile	Ser	aac Asn 780	Ile	Val	Phe	Thr	2352
	785	Leu	Phe	Ala	Leu	Glu 790	Met	Leu	Leu	Lys	Leu 795	ctt Leu	Val	Tyr	Ğİy	Pro 800	2400
45	Phe	GIÀ	Tyr	Ile	Lys 805	Asn	Pro	Tyr	Asn	Ile 810	Phe	gat Asp	Gly	Val	Ile 815	Val	2448
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30	gac Asp	aga Arg	aag Lys 995	aag Lys	cgc Arg	ttg Leu	Ala	ctg Leu 1000	gtg Val	gct Ala	ttg Leu	Gly	gaa Glu LOO5	cac His	gcg Ala	gaa Glu	3024
35	Leu	cga Arg L010	aag Lys	agc Ser	ctt Leu	Leu	cca Pro LO15	ccc Pro	ctc Leu	atc Ile	Ile	cat His 1020	acg Thr	gct Ala	gcg Ala	aca Thr	3072
4 0	cca Pro 1025	Met	tca Ser	cac His	ccc Pro	aag Lys 1030	agc Ser	tcc Ser	agc Ser	Thr	ggt Gly 1035	gtg Val	ggg Gly	gaa Glu	Ala	ctg Leu 1040	3120
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10	cgg age tot gos tot gag cas caa gas tgt aat ggs aag tog got toa Arg Ser Ser Ala Ser Glu His Gln Asp Cys Asn Gly Lys Ser Ala Ser 1170 1175 1130	3552
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	gcc tgg gtc aga tcc cgg ctt cct gcc tgt tgc cga gag cga gat tcc Ala Trp Val Arg Ser Arg Leu Pro Ala Cys Cys Arg Glu Arg Asp Ser 1220 1225 1230	3696
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35	atc ttc ctc aac tgt atc acc atc gct atg gag cgc ccc aaa att gac Ile Phe Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp 1265 1270 1275 1280	3840
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	gat ggg ctg gat gct gtg ggt gtg gat cag cag ccc atc atg aac cac Asp Gly Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His 1475 1480 1485	4464
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60	Glu His Tyr Gln Gln Pro Gln Ile Leu Asp Glu Ala Leu Lys Ile Cys 1620 1625 1630	4896
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	agc cct Ser Pro 1890	aag Lys	cct Pro	G1 y ggg	Ala	cca Pro 895	cac His	acc Thr	act Thr	Ala	cac His 900	att Ile	gga Gly	gca Ala	gcc Ala	5712

	tog ggo tto top ott gag cac cop acg atg gta opp cac cop gag gag Ser Gly Phe Ser Leu Glu His Pro Thr Met Val Pro His Pro Glu Glu 1905 1910 1915 1920	5760
5	gtg cca gtc ccc cta gga cca gac ctg ctg act gtg agg aag tct ggt Val Pro Val Pro Leu Gly Pro Asp Leu Leu Thr Val Arg Lys Ser Gly 1925 1930 1935	5808
10	gtc ago ogg acg cac tot otg occ aat gac ago tac atg tgc ogc aat Val Ser Arg Thr His Ser Leu Pro Asn Asp Ser Tyr Met Cys Arg Asn 1940 1945 1950	5856
15	ggg agc act gct gag aga tcc cta gga cac agg ggc tgg ggg ctc ccc Gly Ser Thr Ala Glu Arg Ser Leu Gly His Arg Gly Tro Gly Leu Pro 1955 1960 1965	5904
20	aaa goo cag toa ggo too ato ttg too gtt cac too caa coa goa gac Lys Ala Gln Ser Gly Ser Ile Leu Ser Val His Ser Gln Pro Ala Asp 1970 1975 1980	5952
-:	acc age tgc atc cta cag ctt ccc aaa gat gtg cac tat ctg ctc cag Thr Ser Cys Ile Leu Gln Leu Pro Lys Asp Val His Tyr Leu Leu Gln 1985 1990 1995 2000	6000
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	cgg Arg	aga Arg	cac His	Ser	att Ile 2165	gct Ala	gtc Val	ag: Ser	Cys	ctg Leu 2170	gac Asp	agc Ser	G17 ggs	Ser	caa Gln 2175	cc: Pro	6528
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45	cgt Arg	agc Ser	ttc Phe	acg Thr 20	cag Gln	ctc Leu	aac Asn	gac Asp	ctg Leu 25	tcc Ser	Gly ggg	gcc Ala	ggg Gly	ggc Gly 30	cgg Arg	cag Gln	96
50	ggg Gly	ccg Pro	ggg Gly 35	tcg Ser	acg Thr	gaa Glu	aag Lys	gac Asp 40	ccg Pro	ggc Gly	agc Ser	gcg Ala	gac Asp 45	tcc Ser	gag Glu	gcg Ala	144
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- -												aaa Lys					1008
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66

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15					gag Glu 405												1248
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35					tca Ser 485									Leu			1488
33	cac His	cat His	cac His	cac His 500	cac His	cat His	cac His	cac His	tac Tyr 505	cac His	ctg Leu	ggt Gly	aat Asn	ggg Gly 510	acg Thr	ctc Leu	1536
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30						gtg Val											2208
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25	atc cct aaa Ile Pro Lys 1985	cta ccc cca Leu Pro Pro 1990	Pro Gly A	egc tcc cct Arg Ser Pro 1995	ctg gct cag Leu Ala Gln	agg cct 6000 Arg Pro 2000
30	ctc agg cgc Leu Arg Arg	cag gca gca Gln Ala Ala 2005	ata agg a Ile Arg T	ct gac tcc Thr Asp Ser 2010	Leu Asp Val	cag ggc 6048 Gln Gly 2015
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	Leu As 2145	sp Ser	Gly		Gln 2150	Pro	Arg	Leu	_	Pro 2155	Ser	Pro	Ser		Leu 2160	
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15	ccc cc Pro Pr		Ser			Val					Arg					6624
15	gac to Asp Se 221	er Lys			Ser					Leu						6672
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	<213>	Homo	sapı	ens					•	• '			•		-	
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10	ctg aag ctg gta Leu Lys Leu Val 1665	e gca ttt ggg L Ala Phe Gly 1670	Phe Arg Arg	tto tto aag gao a Phe Phe Lys Asp 2 675	agg tgg 5040 Arg Trp 1680
	aac cag ctg gad Asn Gin Leu Asg	c ctg gcc atc Leu Ala Ile 1685	gtg ctg ctg Val Leu Leu 1690	tca ctc atg ggc a Ser Leu Met Gly 1	atc acg 5088 Ile Thr 695
15	ctg gag gag ata Leu Glu Glu Ile 1700	Glu Met Ser	gcc gcg ctg Ala Ala Leu 1705	ccc atc aac ccc a Pro Ile Asn Pro 1 1710	acc atc 5136 Thr Ile
20	atc cgc atc atc Ile Arg Ile Met 1715	: Arg Val Leu	cgc att gcc Arg Ile Ala .720	cgt gtg ctg aag o Arg Val Leu Lys I 1725	ctg ctg 5184 Leu Leu
25	aag atg gct acg Lys Met Ala Thr 1730	ggc atg cgc Gly Met Arg 1735	gcc ctg ctg Ala Leu Leu	gac act gtg gtg o Asp Thr Val Val (1740	caa gct 5232 Gln Ala
30	ctc ccc cag gto Leu Pro Gln Val 1745	ggg aac ctg Gly Asn Leu 1750	Gly Leu Leu	ttc atg ctc ctg t Phe Met Leu Leu E 755	ett ttt 5280 Phe Phe 1760
	atc tat gct gcc Ile Tyr Ala Ala	ctg gga gtg Leu Gly Val	gag ctg ttc (Glu Leu Phe (1770	ggg agg ctg gag t Gly Arg Leu Glu C 17	gc agt 5328 Cys Ser 775
35	gaa gac aac ccc Glu Asp Asn Pro 1780	Cys Glu Gly	ctg agc agg o Leu Ser Arg I 1785	cac gcc acc ttc a His Ala Thr Phe S 1790	agc aac 5376 Ser Asn
40	ttc ggc atg gcc Phe Gly Met Ala 1795	Phe Leu Thr	ctg ttc cgc o Leu Phe Arg v 800	gtg too acg ggg g Val Ser Thr Gly A 1805	gac aac 5424 Asp Asn
45	tgg aac ggg atc Trp Asn Gly Ile 1810	atg aag gac a Met Lys Asp ' 1815	acg ctg cgc o	gag tgc tcc cgt g Glu Cys Ser Arg G 1820	gag gac 5472 Slu Asp
50	aag cac tgc ctg Lys His Cys Leu 1825	agc tac ctg of Ser Tyr Leu 1 1830	Pro Ala Pro S	teg eee gte tae t Ser Pro Val Tyr F 335	tc gtg 5520 Phe Val 1840
	Thr Phe Val Leu	gtg ccc cag t Val Pro Gln 1 1845	ttc gtg ctg o Phe Val Leu v 1850	gtg aac gtg gtg g /al Asn Val Val V . 18	rtg gcc 5568 Val Ala 155
<i>55</i>	gtg ctc atg aag Val Leu Met Lys 1860	His Leu Glu (gag agc aac a Glu Ser Asn I 1865	aag gag get egg g Lys Glu Ala Arg G 1870	yag gat 5616 ilu Asp
60	gcg gag ctg gac Ala Glu Leu Asp 1875	Ala Glu Ile (gag ctg gag a Glu Leu Glu N 880	atg gcg cag ggc c Met Ala Gln Gly P 1885	cc.ggg 5664 Pro Gly
	agt gca cgc cgg Ser Ala Arg Arg	gtg gac gcg (Val Asp Ala A	gac agg cet o Asp Arg Pro E	ccc ttg ccc cag g Pro Leu Pro Gìn G	ag agt 5712 lu Ser

	1890	. :	1895	. 1	1900	
5	ccg ggc gcc Pro Gly Ala 1905	agg gac gcc Arg Asp Ala 1910	cca aac o Pro Asn i	ctg gtt gca Leu Val Ala 1915	cgc aag gtg : Arg Lys Val :	ccc gtg 5760 Ser Val 1920
	tcc agg atg Ser Arg Met	ctc tcg ctg Leu Ser Leu 1925	ccc aac : Pro Asn A	gac agc tac Asp Ser Tyr 1930	atg tto agg (Met Phe Arg)	ccc gtg 5808 Pro Val 935
10	gtg cct gcc Val Pro Ala	tcg gcg ccc Ser Ala Pro 1940	His Pro A	cgc ccg ctg Arg Pro Leu 945	cag gag gtg (Gln Glu Val (1950	gag atg 5856 Glu Met
15	gag acc tat Glu Thr Tyr 1955	Gly Ala Gly	acc ccc Thr Pro	ttg ggc tcc Leu Gly Ser	gtt gcc tct o Val Ala Ser 1 1965	gtg cac 5904. Val His
20	tct ccg ccc Ser Pro Pro 1970	Ala Glu Ser	tgt gcc : Cys Ala : 1975	Ser Leu Gln	atc cca ctg (Ile Pro Leu 7 1980	gct gtg 5952 Ala Val
25	tcg tcc cca Ser Ser Pro 1985	gcc agg agc Ala Arg Ser 1990	ggc gag Gly Glu	ccc ctc cac Pro Leu His 1995	gcc ctg tcc Ala Leu Ser	cct cgg 6000 Pro Arg 2000
	ggc aca gcc Gly Thr Ala	c cgc tcc ccc A Arg Ser Pro 2005	agt ctc Ser Leu	agc cgg ctg Ser Arg Leu 2010	ctc tgc aga Leu Cys Arg	cag gag 6048 Gln Glu 015
30	gct gtg cac Ala Val His	acc gat tcc Thr Asp Ser 2020	Leu Lys	gga aga ttg Gly Arg Leu 025	aca gcc cta Thr Ala Leu 2030	ggg aca 6096 Gly Thr
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45	<220> <221> CDS <222> (1).	.(6114)	·	•		
50	<400> 10 atg acc ga Met Thr Gl 1	g ggc gca cgg u Gly Ala Arg 5	gcc gcc Ala Ala	gac gag gtc Asp Glu Val 10	cgg gtg ccc Arg Val Pro	ctg ggg 48 Leu Gly 15
<i>55</i>	cgc cgc cc Arg Arg Pr	c tgg ccc tgc o Trp Pro Cys 20	ggc gtt Gly Val	ggt ggg ggc Gly Gly Gly 25	gtc ccc gga Val Pro Gly 30	gag ccc 96 Glu Pro
60	cgg ggc gc Arg Gly Al	a Gly Thr Arg	ggc gga Gly Gly 40	ggg ggg ttc Gly Gly Phe	gag ctc ggc Glu Leu Gly 45	gtg tca 144 Val Ser
	ccc tcc ga Pro Ser Gl 50	g agc ccg gcg u Ser Pro Ala	g gcc gag Ala Glu 55	cgc tgc gcg Arg Cys Ala	g gag ctg ggt Glu Leu Gly 60	gcc gac 192 Ala Asp

5	gag Glu 65	Glu	cag Gln	cgc Arg	gt: Val	ccg Pro 70	tac Tyr	ccg Pro	gcc Ala	ttg Leu	gog Ala 75	Ala	acg Thr	gtc Val	ttc Phe	ttc Phe 80	240
-	tgc Cys	ctc Leu	gg: Gly	cag Gln	acc Thr 35	acg Thr	cgg Arg	ccg Pro	cgc Arg	agc Ser 90	Trp	tgc Cys	Leu	cgg Arg	ctg Leu 95	gtc Val	288
10	tgc Cys	aac Asn	cca Pro	tgg Trp 100	ttc Phe	gag Glu	cac His	gtg Val	agc Ser 105	atg Met	ctg Leu	gta Val	atc Ile	atg Met 110	Leu	aac Asn	336
15	tgc Cys	gtg Val	acc Thr 115	ctg Leu	ggc Gly	atg Met	ttc Phe	cgg Arg 120	ccc Pro	tgt Cys	gag Glu	gac Asp	gtt Val 125	gag Glu	tgc Cys	ggc Gly	384
20	tcc Ser	gag Glu 130	cgc Arg	tgc Cys	aac Asn	atc Ile	ctg Leu 135	gag Glu	gcc Ala	ttt Phe	gac Asp	gcc Ala 140	ttc Phe	att Ile	ttc Phe	gcc Ala	432
25	ttt Phe 145	ttt Phe	gcg Ala	gtg Val	gag Glu	atg Met 150	gtc Val	atc Ile	aag Lys	atg Met	gtg Val 155	gcc Ala	ttg Leu	Gly	ctg Leu	ttc Phe 160	480
	Gly	cag Gln	aag Lys	tgt Cys	tac Tyr 165	ctg Leu	ggt Gly	gac Asp	acg Thr	tgg Trp 170	aac Asn	agg Arg	ctg Leu	gat Asp	ttc Phe 175	ttc Phe	528
30	atc Ile	gtc Val	gtg Val	gcg Ala 180	ggc Gly	atg Met	atg Met	gag Glu	tac Tyr 185	tcg Ser	ttg Leu	gac Asp	gga Gly	cac His 190	aac Asn	gtg Val	576
35	agc Ser	ctc Leu	tcg Ser 195	gct Ala	atc Ile	agg Arg	acc Thr	gtg Val 200	cgg Arg	gtg Val	ctg Leu	cgg Arg	ccc Pro 205	ctc Leu	cgc Arg	gcc Ala	624
40	atc Ile	aac Asn 210	cgc Arg	gtg Val	cct Pro	agc Ser	atg Met 215	cgg Arg	atc Ile	ctg Leu	gtc Val	act Thr 220	ctg Leu	ctg Leu	ctg Leu	gat Asp	672
45	acg Thr 225	ctg Leu	ccc Pro	atg Met	ctc Leu	ggg Gly 230	aac Asn	gtc Val	ctt Leu	ctg Leu	ctg Leu 235	tgc Cys	ttc Phe	ttc Phe	gtc Val	ttc Phe 240	720
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	ccc Pro 305	ggc Gly	cgc Arg	cgc Arg	gac Asp	gtg Val 310	cgc Arg	atg Met	ccc Pro	tgc Cys	acc Thr 315	ctg Leu	ggc Gly	tgg Trp	gag Glu	gcc Ala 320	960

5							gag Glu										1003
÷							tac Tyr										1056
10							aac Asn										1104
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20							tca Ser										1200
<i>25</i>							ttc Phe										1248
							gag Glu										1296
30							cac His							Leu			1344
35							tgc Cys 455										1392
40							aag Lys										1440
45							aag Lys										1488
	cag Gln	ggt Gly	ccc Pro	ggg Gly 500	His	cgc Arg	cag Gln	cgc Arg	cgg Arg 505	gca Ala	ggc Gly	agg Arg	cac His	aca Thr 510	gcc Ala	tcg Ser	1536
50	gtg Val	cac His	cac His 515	ctg Leu	gtc Val	tac Tyr	cac His	cac His 520	cat His	cac His	cac His	cac His	cac His 525	cac His	cac His	tac Tyr	1584
55	cat His	ttc Phe 530	agc Ser	cat His	ggc Gly	agc Ser	Pro 535	cgc Arg	agg Arg	ccc Pro	ggc Gly	ccc Pro 540	gag Glu	cca Pro	ggc Gly	gcc Ala	1632
60	tgc Cys 545	gac Asp	acc Thr	agg Arg	ctg Leu	gtc Val 550	cga Arg	gct Ala	ggc Gly	gcg Ala	ccc Pro 555	ccc Pro	tcg Ser	cca Pro	cct Pro	ser 560	1680
							gac Asp										1728

5	gcc Ala	gac Asp	tgc Cys	cac His 580	ata Ile	gag Glu	ggg	ccg Pro	cag Gln 585	Glu	agg Arg	gcc Ala	Arg	gtg Val 590	Gly	aca Thr	1776
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10	cac His	cat His 610	gaa Glu	cta Leu	ccc Pro	cac His	gat Asp 615	cct Pro	gcc Ala	ctc Leu	·agg Arg	ggt Gly 620	G] À	cag Gln	cgg Arg	caa Gln	1872
15	agg Arg 625	cag Gln	cac His	cag Gln	ccc Pro	cgg Arg 630	acc Thr	caa Gln	G]A aaa	gaa Glu	gtg Val 635	ggc	cgg Arg	tgg Trp	acc Thr	gcc Ala 640	1920
20	agg Arg	cac His	cgg Arg	G] À ààà	cac His 645	ggc Gly	ccg Pro	ttg Leu	agc Ser	ttg Leu 650	aac Asn	agc Ser	cct Pro	gat Asp	ccc Pro 655	tac Tyr	1968
25	gag Glu	aag Lys	atc Ile	ccg Pro 660	cat His	gtg Val	gcc Ala	elà aaa	gag Glu 665	cat His	gga Gly	ctg Leu	ggc Gly	caa Gln 670	gcc Ala	cct Pro	2016
	Gly	His	Leu 675	Ser	Gly	Leu	Ser	Val 680	Pro	Cys	Pro	ctg Leu	Pro 685	Ser	Pro	Pro	2064
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35	Ala 705	Leu	Glu	Asp	Pro	Glu 710	Gly	Glu	Leu	Ser	Gly 715	tcg Ser	Glu	Ser	Gly	Asp 720	2160
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<i>60</i> .	Ala	Ile	Leu	Val	Asn 805	Thr	Leu	Ser	Met	Gly 810	Val	gag Glu	Tyr	His	Glu 815	Gln	2448
•	ccc Pro	gag Glu	gag Glu	ctg Leu 820	act Thr	aat Asn	gct Ala	ctg Leu	gag Glu 325	atc Ile	agc Ser	aac Asņ	atc Ile	gtg Val 830	ttc Phe	acc Thr	2496

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	ctg Leu	ggc Gly 850	tac Tyr	atc Ile	cgg Arg	aac Asn	ccg Pro 855	tac Tyr	aac Asn	atc Ile	ttc Phe	gac Asp 860	ggc Gly	ato Ile	atc Ile	gtg Val	2592
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15												aag Lys					2688
20												gtg Val					2736
25	aac Asn	gtg Val	gct Ala 915	acc Thr	ttc Phe	tgc Cys	acg Thr	ctg Leu 920	ctc Leu	atg Met	ctc Leu	ttc Phe	att Ile 925	ttc Phe	atc Ile	ttc Phe	2784
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30	gac Asp 945	acc Thr	gga Gly	gac Asp	acc Thr	gtg Val 950	cct Pro	gac Asp	agg Arg	aag Lys	aac Asn 955	ttc Phe	gac Asp	tcc Ser	ctg Leu	ctg Leu 960	2880
35												cag Gln					2928
40												tcc Ser					2976
45	tac Tyr	ttc Phe	gtg Val 995	gcc Ala	ctc Leu	atg Met	Thr	ttc Phe .000	ggc Gly	aac Asn	tat Tyr	gtg Val 1	ctc Leu .005	ttc Phe	aac Asn	ctg Leu	3024
	Leu	gtg Val .010	gcc Ala	atc Ile	ctc Leu	Val	gag Glu 015	ggc Gly	ttc Phe	cag Gln	Ala	gag Glu .020	ggc Gly	gat Asp	gcc Ala	aac Asn	3072
50		Ser			Asp					Ser		cac His			Glu		3120
55				Leu					Thr			ctg Leu		Met			3168
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	gca gca gca gct Ala Ala Ala Ala 1105	ccg ggg acc co Pro Gly Thr An 1110	gc cac tgg gag rg His Trp Glu 1115	acc aga agc ctc c Thr Arg Ser Leu A 11	gg 3360 rg 20
10	Gin Pro Pro Lys	tto too ôtg to Phe Ser Leu Cy 125	gc ccc ctg ggg ys Pro Leu Gly 1130	ccc agt ggc gcc t Pro Ser Gly Ala T 1135	rp
15	agc agc cgg cgc Ser Ser Arg Arg 1140	tcc agc tgg ac Ser Ser Trp Se	gc agc ctg ggc er Ser Leu Gly 1145	cgt gcc cag cct c Arg Ala Gln Pro G 1150	aa 3456 ln
20	gcg ccg gcg tgc Ala Pro Ala Cys 1155	cag tgt ggg ga Gìn Cys Gly Gl 116	lu Arg Glu Ser	ctg ctg tct ggc g Leu Leu Ser Gly G 1165	ag 3504 lu
25	1170	Thr Asp Asp Gl 1175	u Ala Glu Asp 1	ggc agg gcg cgc t Gly Arg Ala Arg S 180	er
	ggg ccc cgt gcc o Gly Pro Arg Ala ' 1185 :	acc cca ctg cg Thr Pro Leu Ar 1190	gg cgg gcc gag rg Arg Ala Glu : 1195	tcc ctg gac cca c Ser Leu Asp Pro A 12	rg
30	Pro Leu Arg Arg	ccg cct ccc go Pro Pro Pro Al 205	c tac caa gtg o a Tyr Gln Val i 1210	ege gat ege gae g Arg Asp Arg Asp G 1215	gg 3648 ly
35	Gin Val Val Ala 1 1220	Leu Pro Ser As	p Phe Phe Leu 1 1225	ege ate gae age ca Arg Ile Asp Ser H. 1230	is
40	1235	Ala Glu Leu As 1 [.] 24	p Asp Asp Ser (gag gac agc tgc to Glu Asp Ser Cys Cy 1245	ys
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	agc agg agg cct of Ser Arg Arg Pro 0 1265	ggg ccc tct ac Sly Pro Ser Th 1270	c ctc tac ctc t r Leu Tyr Leu E 1275	itc tcc cca cag as Phe Ser Pro Gln As 128	3840 sn 30
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55	cac gtg gtc ctc g His Val Val Leu V 1300	rtc ttc atc tt /al Phe Ile Ph	c ctc aac tgc q e Leu Asn Cys \ 1305	gtc acc atc gcc ct Val Thr Ile Ala Le 1310	g 3936 eu
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	gtc tcc aat tac a Val Ser Asn Tyr I 1330	ite tte acg ged le Phe Thr Ala 1335	a Ile Phe Val A	jcg gag atg atg gt Mat Met Met Va 140	g 4032 il

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15	gtt Val	Leu	cgc Arg 1395	gtg Val	ctg Leu	cgt Arg	Leu	ctg Leu 1400	Arg	acc Thr	ctg Leu	Arg	cct Pro 1405	ctg Leu	agg Arg	gtc Val	4224
20	Ile	agc Ser 1410	cgg Arg	gcc Ala	ccg Pro	Gly	ctc Leu L415	aag Lys	ctg Leu	gtg Val	Val	gag Glu 1420	acg Thr	ctg Leu	ata Ile	tca Ser	4272
25	tca Ser 1425	Leu	agg Arg	ccc Pro	att Ile	ggg Gly L430	aac Asn	atc Ile	gtc Val	Leu	atc Ile 1435	tgc Cys	tgc Cys	gcc Ala	Phe	ttc Phe 1440	4320
	atc Ile	att Ile	ttt Phe	Gly	att Ile 1445	ttg Leu	ggt Gly	gtg Val	Gln	ctc Leu 1450	ttc Phe	aaa Lys	Gly	Lys	ttc Phe 1455	tac Tyr	4368
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ō	Arg	Trp	Ile	His	Ser 1605	ctg Leu	Cys	Thr	Ser	His 1610	Tyr	Leu	Asp	Leu	Phe 1615	Ile	4848
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	atc gag c Ile Glu L 18	eu Glu Me	g gcg c t Ala G	ag ggd ln Gly 1880	/ Pro Gi	g agt 7 Ser	gca cgc Ala Arg 1885	cgg gto Arg Val	g gac L Asp	5664
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35	ggc gag cc Gly Glu Pr 1985	o Leu His	1990	u Ser	Pro Arq	1995	Thr.Ala	Arg Ser	Pro 2000	6000
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	gct Ala	gag Glu	cca Pro	gga Gly 20	gtc Val	acc Thr	acg Thr	gag Glu	cag Gln 25	occ Pro	gga Gly	ccc Pro	cgg Arg	ago Ser 30	ccc Pro	cca Pro	96
5	tc: Ser	tcc Ser	ccg Pro 35	cca Pro	ggc Gly	ctg Leu	gag Glu	gag Glu 40	510 CCf	ctg Leu	gat Asp	gga Gly	got Ala 45	gat Asp	cct Pro	cat His	144
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	G1 y	gac Asp	aat Asn 275	. Giy	ata Tle	atg Met	ggc Gly	tgc Cys 280	: His	gag Glu	ato Ile	coc Pro	285	Leu	aaçı Lys	g gag s Glu	864
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15	ctc Leu	GJÀ āàā	gtg Val	Glu	ctc Leu 1605	ttt Phe	Gly ggg	aag Lys	Leu	gtc Val 1610	tgc Cys	aac Asn	gac Asp	Glu	aac Asn 1615	ccg Pro	4848
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20	gag Glu	ccg	gga Gly	atc Ile 20	act Thr	gag Glu	cag Gln	ccg Pro	ggg Gly 25	ccc Pro	cgg Arg	agt Ser	ccc Pro	cct Pro 30	cca Pro	tcc Ser	96
25	cct Pro	cca Pro	ggc Gly 35	ctg Leu	gag Glu	gag Glu	cca Pro	ttg Leu 40	gaa Glu	gga Gly	acc Thr	aac Asn	cct Pro 45	gac Asp	gtc Val	cca Pro	144
30	cat His	cca Pro 50	gac Asp	ctg Leu	gct Ala	cct Pro	gtt Val .55	gct Ala	ttc Phe	ttc Phe	tgc Cys	ctg Leu 60	cgc Arg	cag Gln	acc Thr	acg Thr	192
35	agc Ser 65	cca Pro	cgg Arg	aac Asn	tgg Trp	tgc Cys 70	atc	aag Lys	atg Met	gtt Val	tgt Cys 75	aac Asn	ccg Pro	tgg Trp	ttc Phe	gag Glu 80	240
	tgt Cys	gtg Val	agc Ser	atg Met	ctg Leu 85	gtt Val	att Ile	ctg Leu	ctg Leu	aac Asn 90	tgt Cys	gtg Val	acc Thr	ctg Leu	ggc Gly 95	atg Met	288
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55	gga Gly 145	gac Asp	aca Thr	tgg Trp	aac Asn	cgc Arg 150	ctg Leu	gat Asp	ttc Phe	ttc Phe	att Ile 155	gtc Val	atg Met	gca Ala	GJ À GG À	atg Met 160	480
	gtt Val	gag Glu	tac Tyr	tct Ser	ctg Leu 165	gac Asp	cta Leu	cag Gln	aac Asn	atc Ile 170	aac Asn	ctg Leu	tca Ser	gcc Ala	atc Ile 175	cgc Arg	528
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13												tcc Ser					816
20												ctg Leu					864
25												gac Asp 300					912
30												aac Asn					960
35												cac His					1008
33												att Ile					1056
40												gtg Val					1104
45												atc Ile 380					1152
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. 33												gag Glu					1296
60 .		Ğlu										ctt Leu					1344
	cgc	cgt	gcc	cta	ggc	ctc	tac	cag	gcc	ctg	cag	aac	cgg	cgc	cag	gcc	1392

	Arg	Arg 450	Ala	Leu	Gly	Leu	Tyr 455	Gln	Ala	Leu	Gln	Asn 460	Arg	Arg	Gln	Ala	
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10				cac His													1488
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55				gaa Glu													2064
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15	gga Gly	gac Asp	acc Thr 755	gtt Val	cct Pro	gac Asp	agg Arg	aag Lys 760	aac Asn	ttc Phe	gat Asp	tcc Ser	tta Leu 765	ctg Leu	tgg Trp	gcc Ala	2304
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	His	s Gl	u Se	r Le	u Let 965	u Sei	c Gl	y Glu	ي Gl	y Gl	y Gl	y Se:	r Cys	s va	l Ar 97	g Ala	
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	Ser V	/al		Ser 1220	Ala	Gly	Gly		Lys 1225	Ile	Leu	Gly		Leu 1230	Arg	Va!	
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25	tac c Tyr A	.rg '	tgg Trp 315	gtg Val	cat His	cac His	Lys	tac Tyr 1320	aac Asn	ttt Phe	gac Asp	Asn	ctg Leu 1325	ggc Gly	cag Gln	gca Ala	3984
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	ccc atc aac ccc acc atc atc cgt atc atg cgt gtt ctg cgt atc Pro Ile Asn Pro Thr Ile Ile Arg Ile Met Arg Val Leu Arg Ile 1540 1545 1550	c gcc 4656 e Ala
20	cgg gtg ttg aag cta ttg aag atg gcc aca gga atg cgg gcc ctc Arg Val Leu Lys Leu Lys Met Ala Thr Gly Met Arg Ala Leu 1555 1560 1565	g ctg 4704 u Leu
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	ecc tge ecc tge ecc tge ecc tgt get gge ecg agg etg ecc act	agt 5232

	Pro Cys 1730	STO	Cys	Pro		Pro 1735	Cys	Ala	Gly		Arg 1740	Leu	Pro	Thr	Ser	
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 10	gac acc Asp Thr	gag Glu	Ser	cac His 1765	ctg. Leu	tgc Cys	cgg Arg	His	tgc Cys 1770	tat Tyr	tct Ser	cca Pro	Ala	cag Gln 1775	gag Glu	5328
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13	ggg gag Gly Glu	ctg Leu 1795	acc Thr	atc Ile	att Ile	Asp	aac Asn 1800	ctg Leu	tct Ser	ggg Gly	Ser	gtc Val 1805	ttc Phe	cac His	cac His	5424
20	tac gcc Tyr Ala 1810	tca Ser	cct Pro	gac Asp	Gly	tgt Cys 1815	ggc Gly	aag Lys	tgt Cys	His	cat His 1820	gac Asp	aag Lys	caa Gln	gag Glu	5472
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35	<400> 13 Ile Arg 1		Met	Arg 5	Val	Leu	Arg	Ile	Ala 10	Arg	Val	Leu	Lys	Leu 15	Leu	
	Lys Met	Ala														

INTERNATIONAL SEARCH REPORT

Intern ial Application No

PCT/US 98/23161 A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C12N15/12 C07k CO7K14/705 C07K16/28 C12N5/10 G01N33/68 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Category 1 Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. X WO 95 04144 A (NEUREX CORP) 1,2,7, 9 February 1995 10-18, 20-22 Υ see abstract; claims 1-10 3,19 X NOONEY JM (REPRINT) ET AL: "Identifying 1,2, neuronal non-L Ca2+ channels - more than 10-16, stamp collecting?" 20-22 TRENDS IN PHARMACOLOGICAL SCIENCES, 10-1997, 18, 363-371, XP002093637 see page 369, right-hand column - page 370, right-hand column Further documents are listed in the continuation of box C. Х Patent family members are fisted in annex. Special categories of cited documents: "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the lart which is not considered to be of particular relevance invention earlier document but published on or after the international "X" document of particular relevance; the claimed invention filing date cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document which may throw doubts on pnority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu-"O" document referring to an oral disclosure, use, exhibition or other means ments, such combination being obvious to a person skilled in the art. document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 16 February 1999 09/03/1999 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl. Fax: (+31-70) 340-3016 Gurdjian, D

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